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CANCER OF THE MAMMARY GLANDS INDUCED IN MALE MICE RECEIVING ESTROGENIC HORMONE

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Though mammary cancer develops spontaneously in female mice of certain strains, it seldom or never occurs in males. The mammary rudiments of the male mouse undergo little, if any, development after the weaning age (Gardner, Diddle, Allen and Strong [1]). Feminization of the male mouse by ovarian grafts has been found to induce a partial growth of the mammary glands (Gardner [2]) and to induce a development of tumors as frequently as in virgin female mice of the same strain (Murray [3]). Lacassagne [4] observed that mammary cancer could be induced in male mice receiving estrogenic hormone over an extended period. Burrows [5] made similar observations on two mice and Bonser [6] on three mice. The development of mammary cancer thus appears to be a sex-limited character in the mouse, depending on either (1) the feminizing effect of the female sex hormone in the induction of growth of the mammary gland to serve as a substratum for the differentiation

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1. Gardner, W. U.; Diddle, A. W.; Allen, E., and Strong, L. C.: Anat. Rec. **60**:457, 1934.
2. Gardner, W. U.: Endocrinology **19**:656, 1935.
3. Murray, W. S.: J. Cancer Research **12**:18, 1928.
4. Lacassagne, A.: Compt. rend. Acad. d. sc. **195**:630, 1932.
5. Burrows, H.: Am. J. Cancer **24**:613, 1935.
6. Bonser, G. M.: J. Path. & Bact. **41**:217, 1935.

of growth of cancer or (2) a specific agent stimulating unrestricted mammary growth.

The present report relates further observations of mammary tumors arising in male mice during the course of the administration of estrogenic hormone.

EXPERIMENTS

The estrogenic hormone (keto-estrin benzoate [7]) used was prepared from the urine of pregnant women. Six male mice from one litter were given weekly injections of 500 international units of the hormone, beginning at 28 days of age and extending for periods of from one hundred and one to one hundred and ninety-nine days. All the injections were made subcutaneously. The mice were from a strain (A) [8] in which spontaneous mammary cancer develops in more than 80 per cent of the females. They were kept under regular laboratory conditions on a diet of Purina Fox Chow.

The mice tolerated the treatment well for several months, though body growth was slightly retarded. After from six to eight weeks bilateral scrotal hernia developed in five of the mice, and a unilateral hernia developed in one. One mouse was killed after treatment for fourteen weeks; another died after nineteen weeks of treatment. Two mice were killed at twenty-three weeks, another at twenty-four weeks and another at twenty-eight weeks after treatment was begun. The scrotal hernias of the three mice treated for twenty-three and twenty-four weeks regressed a week or so before death. Following the regression of size of the hernias a marked hydronephrosis developed. The mice then became emaciated and were removed. Carcinoma developed in two mice which were treated for twenty-three weeks with the keto-estrin benzoate. Two large mammary tumors developed in one mouse, and one small tumor developed in a second mouse. A detailed account of the observations on these two animals follows:

Mouse 1.—A tumor was palpated in the lateral axillary region on the left side after twenty-one weeks of treatment. The tumor (B) at this time was about 4 mm. in diameter; it approximately doubled its size during the next fifteen days, after which time it was partially removed for biopsy and grafted into twelve mice of a similar strain. The second tumor (A), located anterior to the right axilla in the region of the neck, was first noticed ten days after the first tumor and grew very rapidly. It was larger than the first tumor when removed, three days after its discovery. Twelve mice of the same strain (A) and two mice of

7. The preparation used in this work was benzogynoestryl—C_6H_5COO ($C_{18}H_{21}O$)—which was obtained through Dr. Girard, of Paris, from the Laboratoire Française de Chimiothérapie, of Paris, at the request of Dr. G. M. Smith. (This is presumably the substance that was used by Lacassagne, which he called "folliculin benzoate.") The active chemical was keto-estrin benzoate (3-benzoate-17-keto-1, 3, 5-estratriene), which was prepared from ketohydroxyestrin derived from the urine of pregnant women. It was obtained in solution in oil (10,000 international units per cubic centimeter.

8. This strain was developed by Dr. L. C. Strong, who has observed the incidence of cancer during about fifty generations in which intensive inbreeding has been practiced.

a second strain (CBA) received grafts of the tumor tissue. The mouse was killed two days later at 190 days of age.

Both tumors were microscopically adenocarcinomas. In general, they were composed of both solid masses and cords of polygonal cells, commingling with areas of small, compact, delicate acini (figs. 1 *A, C* and *D*). They were morphologically similar to the spontaneous mammary tumors occurring in female mice of this strain as described recently by Williams, Silcox and Halpert.[9] Several small ducts slightly distended with a homogeneous secretion were noted (fig. 1 *A*). There were no cysts, either of the simple or of the hemorrhagic type. Mitotic figures were frequent. The supporting stroma was, as a rule, delicate, yet in places it was thickened. Numerous blood vessels were scattered through the tumor. There was no evidence of hemorrhage, necrosis or leukocytic infiltration. The experimental grafts of both tumors structurally resembled the original growths (fig. 1 *B*).

Mouse 2.—The tumor, measuring about 3 mm., was not observed until after the mouse was killed at 193 days of age.

This tumor was a small adenocarcinoma (fig. 2 *A*) resembling in detail the structure of the tumor of mouse 1, which has already been described. It was somewhat more compact, with very little connective tissue. Mitotic figures were plentiful. There were no cysts.

Fragments of both tumors of mouse 1 grew readily when grafted into the axillary region of all other mice of the same strain. Some of the grafts grew more rapidly than others. Within three weeks four of the fourteen mice bearing grafts of the second tumor of mouse 1 carried tumors equal in size to the tumor of the donor. The grafts in the other mice grew less rapidly, requiring more than four weeks to reach a similar size. The sex of the recipients did not influence the rate of growth of the grafted tumors. Pregnancy likewise produced no observable changes in the rate of growth of the grafts. In two mice from an unrelated strain (CBA) the grafts failed to grow.

In addition to the six male mice of the A strain, two male mice of the C_3H strain received similar treatment from the time of birth for periods of sixteen and seventeen weeks. Though a mammary tumor did not develop in these mice of the C_3H strain, the extent and pattern of growth induced in the mammary glands were comparable to those of the mice of the A strain.

The growth of the mammary glands induced by the keto-estrin benzoate with the dose used was abnormal (Gardner, Smith and Strong[10]); that is, it was unlike that observed in normal female mice or in male mice bearing ovarian grafts or receiving injections of theelin in aqueous solution. The normal development of the glands of virgin mice (fig. 3 *D*) was limited to a proliferation of an extensive, branching system of ducts (Gardner and Strong[11]). Theelin and ovarian grafts

9. Williams, A. C.; Silcox, L. E., and Halpert, B.: Am. J. Cancer **24**:823, 1935.

10. Gardner, W. U.; Smith, G. M., and Strong, L. C.: Proc. Soc. Exper. Biol. & Med. **33**:148, 1935.

11. Gardner, W. U., and Strong, L. C.: Am. J. Cancer **25**:282, 1935.

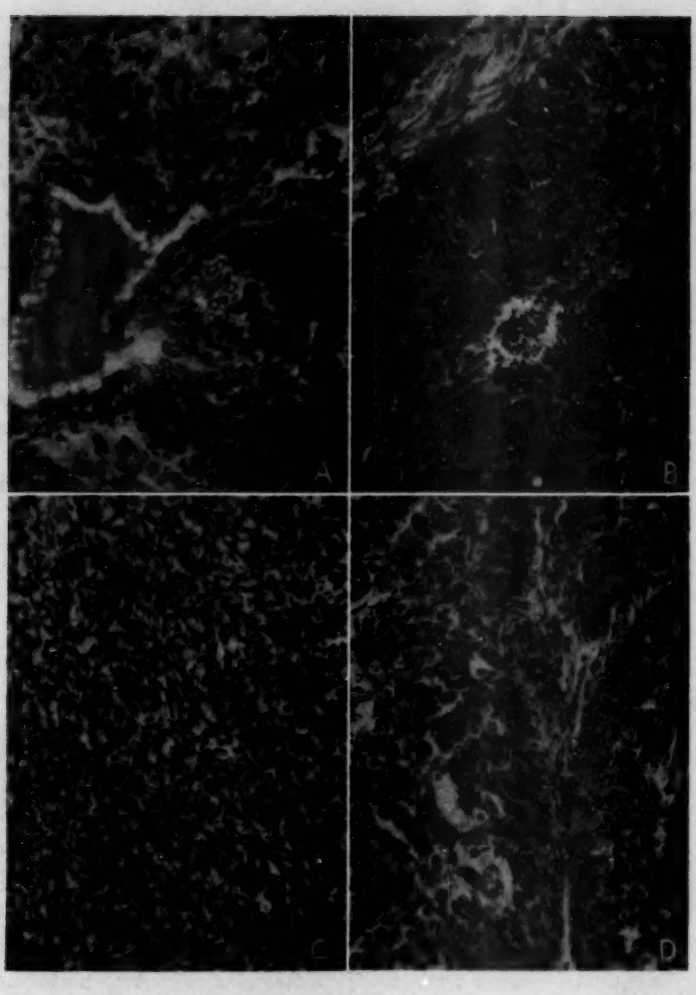

Fig. 1.—*A*, photomicrograph of a section of the mammary tumor A observed in male mouse 1 of the A strain at 185 days of age and removed two days later. The tumor consisted of cords of cylindric and polygonal cells. Several ducts showing a more or less organized epithelium and containing secretion were observed. Connective tissue separated the cords of epithelial cells. Magnification, 250 ×. *B*, photomicrograph of a section of a grafted tumor obtained from the tumor shown in *C* and *D*. A small section of the tumor was grafted into eight male and two female mice of the same strain. All the grafts grew. The tissue just referred to was removed after eighteen days, at which time it was more than 1 cm. in diameter. The grafted tissue was composed of large masses and cords of epithelial cells separated by thick bands of connective tissue. Magnification, 250 ×. *C*, photomicrograph of a section of mammary tumor B arising spontaneously in the mammary glands of the male mouse 1. This tumor was first observed one hundred and forty-five days after treatment was begun. A portion of the tumor was made up of very small acini. A very delicate connective tissue separated the acini. Magnification, 250 ×. *D*, photomicrograph of another area of the mammary tumor B arising spontaneously in the mammary glands of the male mouse 1. The tissue shown in *C* was also noted in the same tumor. This portion of the tumor consisted of cords of epithelial cells and probably contributed the grafted tissue shown in *B*. Magnification, 250 ×.

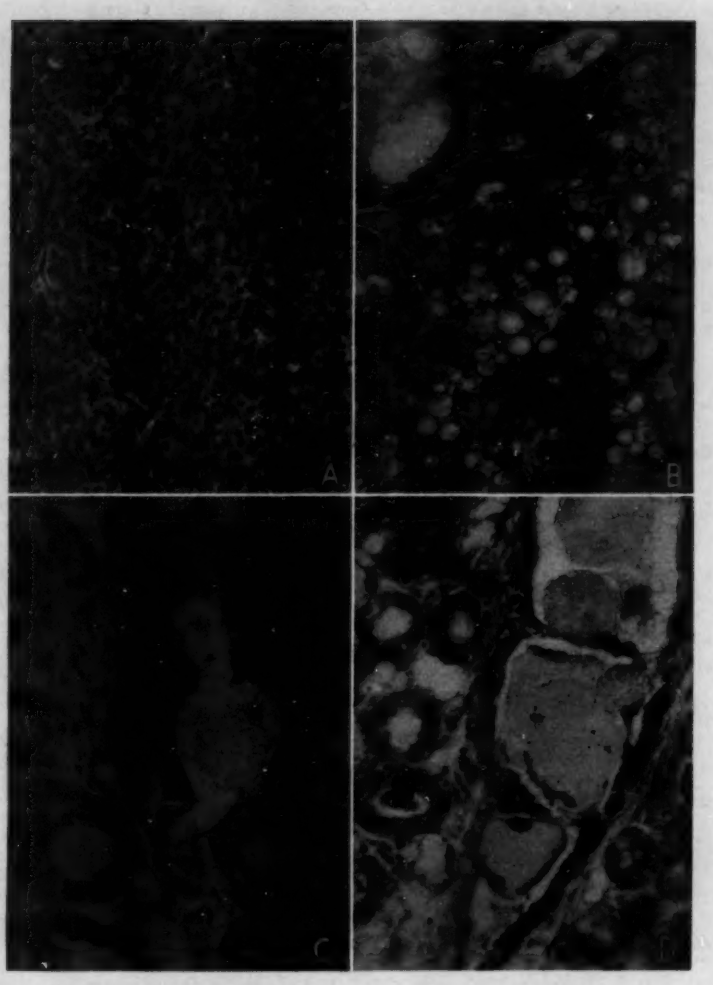

Fig. 2.—*A*, photomicrograph of a section of the small mammary tumor found in male mouse 2 at 193 days of age. This mouse had received 12,000 international units of keto-estrin benzoate during the previous twenty-three weeks. The tumor consisted of a dense mass of epithelial cells separated by septums of delicate connective tissue. Magnification, 250 ×. *B*, photomicrograph of a section of an adenomatous nodule observed in one mammary gland of mouse 1, showing a group of alveoli completely filled with vacuolated epithelial cells. The two mammary cancers shown in figure 1 *A*, *C* and *D* had arisen in other glands. The surrounding alveoli shown at the upper left were normal. Mitotic figures were observed among the vacuolated cells. These vacuolated cells resembled secreting cells in the lactating mammary gland. Magnification, 250 ×. *C*, photomicrograph of an area from another mammary gland of mouse 1. An overgrowth of the mammary stroma had occurred. Some piling up of the epithelial cells was observed in some of the ducts and alveoli of this region. Magnification, 250 ×. *D*, photomicrograph of an area of mammary gland removed from mouse 1. The large duct contained a characteristic concretion-like secretion also found in the breast of mice treated with theelin. Epithelial cells frequently surround the secretion. The mammary stroma in this region was composed of loose fatty connective tissue. Magnification, 250 ×.

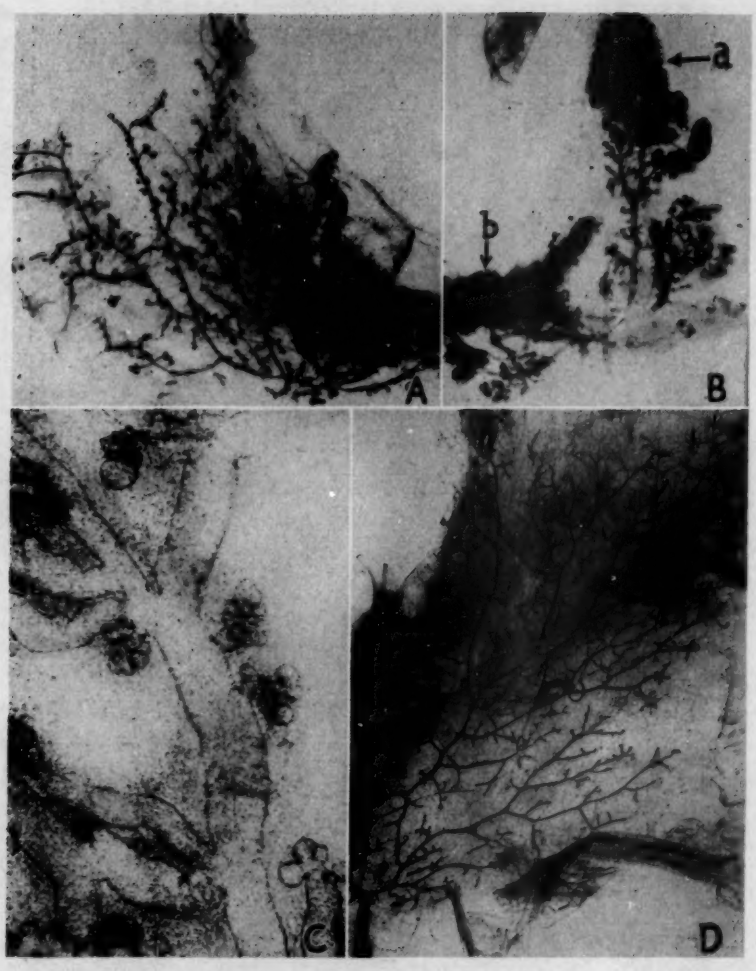

Fig. 3.—*A*, photograph of the greater part of one mammary gland of the second or midthoracic pair from a male mouse of the CBA strain which had carried two ovarian grafts for 372 days. The mammary ducts were very well developed. Many small branches and a few small lobules of alveoli had formed. The condition of the mammary glands was similar to that of male mice receiving injections of theelin. Magnification, 4 ×. *B*, photograph of one mammary gland of the second pair from a mouse of the C$_3$H strain which had received 8,500 international units of keto-estrin benzoate in seventeen weeks. Dense lobules of alveoli (*a*) and (*b*) had developed along the stunted duct system. Other glands of the same mouse and of the other mice used in the present experiment showed a similar extent and type of growth. The photograph may be compared with *A* and *D* to determine the extent of stunting of the duct system and the difference in the pattern of growth. Magnification, 6 ×. *C*, photomicrograph of a portion of the mammary gland seen in *A*, showing the extent to which the details of the mammary condition may be studied by the preparations of "whole gland." Numerous small budlike processes had developed along the large ducts. Magnification, 47 ×. *D*, photograph of a portion of the mammary gland of a virgin female mouse 100 days old. The nipple and primary duct are shown in the lower left-hand corner. The pattern and extent of growth may be compared with those shown in *B*. Magnification, 6.5 ×.

stimulated a similar type of growth in the male mice (fig. 3 *A* and *C*). The extent of development of the ducts induced by the keto-estrin benzoate in the males of these strains was uniformly stunted, resulting in relatively restricted mammary glands (fig. 3 *B*). Associated with the stunted proliferation of the ducts were many small lateral growths from these ducts forming large lobules. Some of these lobules were composed of alveoli distended with secretion and with an active epithelium. Some of these alveoli were completely filled with an ingrowth of vacuolated epithelial cells (fig. 2 *B*). In other lobules the alveoli were small and contained little secretion (fig. 2 *C* and *D*). The alveolar epithelium throughout was in more or less active growth, as determined by the high incidence of mitosis. Some of these lobules resembled diffuse adenomatous growths (fig. 2 *B*). The supporting stroma of the lobules, instead of being a delicate connective tissue containing fat, consisted of dense connective tissue in many portions of the glands (fig. 2 *C*).

COMMENT

Three mammary cancers were observed in two male mice receiving weekly injections of large amounts of keto-estrin benzoate. It is obviously of great importance to determine whether these tumors arose as a result of the feminizing effect of the hormone administered to the male mice genetically susceptible to mammary tumor or whether the hormone administered acted as a specific agent stimulating unrestricted mammary growth.

The estrogenic hormone stimulates a growth of the mammary duct system in male mice in which the mammary rudiments do not develop normally. It seems clear that the hormone used in the present investigation induced an abnormal mammary growth for either qualitative or quantitative reasons. The growth of the duct system was restricted or stunted, while an active growth of the mammary alveoli and connective tissue stroma had occurred. As in the male mice of the same strain bearing ovarian grafts or receiving an aqueous solution of theelin, all the mammary rudiments did not respond. Some of them remained small. The impression is gained, therefore, that the individual male mammary rudiments respond with varying intensities ranging from little or no appreciable growth to an extensive development of the duct system, with proliferation of lobules of alveoli and finally the appearance of irregular shaped adenomas and eventually cancer. Cancer arising in the actively hyperplastic rudiments, as stated, may be regarded as a growth response to keto-estrin benzoate of an extraordinarily increased tempo. Groups of cells in certain areas in rapid cell division assume the biologic characteristics of cancer. The degree of mammary response of the male mice receiving theelin or bearing ovarian grafts in our experience was largely limited to the stimulation of the duct system, though occasionally

small lobules developed (fig. 3 *A*). A further and abnormal growth of the lobules of the mammary gland and finally unrestricted growth of the mammary tissue were induced by the keto-estrin benzoate under the condition of the present experiment.

The tumors were first observed in mice 173 and 193 days of age. This is at least 100 days before the average age of the appearance of tumors in female mice of the same strain and longer before the appearance of tumors in the glands of virgin females. In a group of twenty-four untreated multiparous female mice of the same strain kept under the same dietary conditions tumors developed at from 210 to 417 days of age, or at an average age of 307 days. The mammary cancers thus appeared from twenty to forty days earlier in the treated males than in any of the females whose glands had been subjected to one or more periods of hypertrophy due to pregnancy and suckling.

If the occurrence of the tumors in these mice is to be ascribed to a feminizing effect, it must be considered that a hyperfeminization has occurred in the present experiment. Associated changes in the pelvic symphysis, testes and seminal vesicles also indicate a hyperfeminization, as these tissue changes were not observed in male mice bearing ovarian grafts. The abnormal growth of the mammary glands observed, however, indicated a possible specific carcinogenic effect.

SUMMARY

Two of six male mice from one litter of the A strain were subjected to weekly injections of 500 international units of keto-estrin benzoate in oil. Two carcinomas developed in one mouse and one in a second mouse. The female mice of the A strain are susceptible to spontaneous mammary cancer.

The pattern of mammary growth induced in the male mice receiving keto-estrin benzoate was abnormal in that the growth of the duct system was restricted or stunted and the mammary lobules developed extensively. Areas showing excessive connective tissue were also observed. Some areas of lobular growth indicated the formation of hyperplastic adenomatous nodules.

NOTE.—From the time that this paper was submitted for publication up to Jan. 11, 1936, six more mammary tumors have been observed in male mice receiving keto-estrin benzoate. Three of these tumors have been studied histologically and were similar to the tumors already described. These tumors appeared in mice at ages varying from 162 to 362 days and after the mice had received from 10,000 to 18,000 international units of keto-estrin benzoate. Four of the mice were under 200 days of age at the time that the tumors were observed.

GENITAL STAPHYLOCOCCIC ACTINOPHYTOSIS (BOTRYOMYCOSIS) IN HUMAN BEINGS

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True botryomycosis has hitherto belonged almost exclusively in the realm of veterinary pathology. While this disease is found very frequently in the horse, in which it was first described by Bollinger [1] in 1870, it is found also in the cow and the sheep and less frequently in the dog and the pig; it is only occasionally observed in human beings with chronic osteomyelitis.

In animals the lesions are essentially intradermal and in many instances posttraumatic. Visceral lesions have been observed. The condition becomes chronic, the lesions either remaining localized or spreading. The classic type is represented by the castration fungus (the *champignon de castration*) in the horse. In some countries castration is, or was, produced by garoting the scrotum between wooden rods, producing necrosis of the genitals. The fungus appears in the remaining central stump. At first localized around the vas deferens, the lesions soon extend into the nearby tissues; later they spread in some cases to the regional lymph nodes and the viscera and even become generalized.

Histologically, the lesions are inflammatory and consist of a central focus of polymorphonuclears surrounded by an area of lymphocytes and plasmocytes and by a peripheral zone of dense sclerotic tissue. Peculiar granules surrounded by minute clublike excrescences are embedded in the middle of the polymorphonuclear sheet and are very similar to actinomycotic granules. In the botryomycotic lesions these granules were long a matter of discussion. Bollinger expressed the opinion that they are mycotic elements and called them Zooglea pulmonalis-equi and the lesion pulmomycosis equi, for in his case the lesions were localized in the lungs. Rivolta [2] (1879) said that they are akin to Actinomyces and proposed the name Discomyces equi, replacing it later (in 1887) by Botryomyces, which was accepted and has been used ever since.

From the Anti-Cancer Center of Laval University.

1. Bollinger, O.: Virchows Arch. f. path. Anat. **49**:583, 1870; Deutsche Ztschr. f. Thiermed. **13**:176, 1887.

2. Rivolta, S.: Gior. di anat. e fisiol. **16**:181, 1884.

In 1888 Kitt [3] questioned the mycotic nature of the granules, and the lesions were successively attributed to Botryococcus ascoformans by Kitt and to Micrococcus botryogenes by Rabe.[4] According to the concepts of these authors, these organisms were considered to be akin to but nevertheless distinct from the staphylococcus. The question was finally solved by Magrou [5] in 1914. He demonstrated in a splendid histologic, bacteriologic and experimental study the true staphylococcic nature of these botryomycotic lesions. He proved that Staphylococcus aureus is able to form granules similar to those of actinomycosis and showed that "the actinophytic differentiation in the staphylococcus depends on closely limited biologic conditions." According to Magrou the genesis of the granules and of the clubs in botryomycosis is most probably a process similar to that leading to the formation of the actinomycotic structures. In the case of the staphylococcus it is determined by a special "symbiotic" equilibrium between the germs and the tissues of the host, which depends primarily on the quantity of microbes introduced.

The thorough study of Magrou has definitely fixed the general histologic aspects and the staphylococcic nature of botryomycosis and has contributed a great deal toward lessening the confusion which was created by the erroneous conclusions of Poncet and Dor,[6] who identified some fairly common lesions in man with botryomycosis in animals. These lesions, generally known as granuloma telangiectaticum, pyogenicum or pediculatum, as pseudobotryomycosis and as angioma hyperplasticum, have nothing to do with true botryomycosis. Not only is the proof of their staphylococcic origin lacking, but their histologic features are different from those of animal botryomycosis. They bear the same relation to granulation tissue as the keloid does to cicatricial sclerosis. Poncet and Dor's error has not, however, been completely eradicated (Torlais,[7] Lubarsch [8] and Karsner [9]).

Since the publication of Magrou's work the realm of true botryomycosis has extended further. In 1922 Aynaud [10] showed the caseous suppuration in the sheep (*abcès du mouton; maladie caséeuse*) to be a genuine botryomycosis of an essentially staphylococcic nature and strictly similar to botryomycosis of the horse and other animals.

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3. Kitt, T.: Centralbl. f. Bakt. **3**:177, 1888.
4. Rabe: Deutsche Ztschr. f. Thiermed. **12**:137, 1886; quoted by Magrou.[5]
5. Magrou, J. E.: Les grains botryomycotiques, Thèse de Paris, no. 267, 1914.
6. Poncet, A., and Dor, L.: Arch. gén. de méd. **3**:129, 1900.
7. Torlais, J.: La botryomycose chez l'homme et chez les animaux, Paris, Gaston Doin & Cie, 1922.
8. Lubarsch, O., in Aschoff, L.: Pathologische Anatomie, ed. 7, Jena, Gustav Fischer, 1928, p. 608.
9. Karsner, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 286.
10. Aynaud, M.: Ann. Inst. Pasteur **42**:256, 1928.

In man botryomycosis is extremely rare, unless it has only remained unrecognized. According to Magrou, "perhaps the case described by Kaiser and Gryns [11] in a human" (reported in a publication that is difficult to obtain) "should be considered as an authentic botryomycosis." The origin of the lesions seemed to be in the bone, and the condition appeared to be a fistulous botryomycotic osteomyelitis. In 1918 Masson [12] reported the first definite case of botryomycosis in man, that of a soldier suffering from osteomyelitis due to a fracture of the hip caused by a bombshell. Masson agreed entirely with Magrou but called attention to the peculiar conditions prevailing in his case, in which the bone structure played a rôle in the evolution of the lesions. Fumagalli [13] published in 1928 the reports of two more cases, but they were instances of nontraumatic botryomycotic osteomyelitis.

Including the cases reported by the Dutch authors, the cases of true botryomycosis in man numbered four. All were osteomyelitic, and it seemed that in the human species bone was the only tissue in which these lesions could evolve. However, we have had the opportunity of observing a female patient with botryomycotic lesions which were localized in the external genitals and presented the clinical picture of bartholinitis. The rarity of the finding as well as some nonrelated peculiarities induced us to publish a report of the case.

REPORT OF A CASE

History.—A married white woman, 53 years of age, came to the Anticancer Center of Laval University at the Hôtel-Dieu Hospital, complaining of a tumor in the vulvar region. There were no hereditary or individual antecedents relevant to the actual lesion. The woman was emaciated. She had been hospitalized three years previously, when she was considered to be suffering from chronic fibrous pulmonary tuberculosis.

The vulvar lesion began two months before, with a small painless induration of the vulva which grew slowly, became painful and induced dysuria and pollakiuria. Examination revealed an egg-shaped tumor in the posterior part of the labium majus, the palpation of which was extremely painful. The overlying integument was distended and glossy. The neighboring tissues, especially the vaginal mucosa, were diffusely hardened. A provisional diagnosis of infected cyst of Bartholin's gland was made but was controlled by a biopsy, the result of which will be reported later.

Course.—The application of hot dressings gave only temporary relief. Three months later the tumor had increased in size, was more painful and had infiltrated the anterior, lateral and posterior wall of the vagina and the tissue surrounding the anal orifice. A second biopsy yielded the same result as the first. At that time a specimen for bacteriologic study was secured from the depths of the surgical section, contamination from the surface being carefully avoided. It showed the presence of Staphylococcus aureus and the colon bacillus.

11. Kaiser and Gryns: Geneesk. tijdschr. v. Nederl.-Indië, 1907, vol. 8; quoted by Magrou.[5]

12. Masson, P.: Lyon chir. **15**:230, 1918.

13. Fumagalli, C. R.: Ann. d'anat. path. **4**:513, 1927.

The most varied treatment with staphylophage, antistaphylococcus stock vaccine and autovaccine, thermocauterization and iodine ionization gave only transitory relief. Semipenetrant roentgen therapy likewise failed. The spread of the induration on the surface and in the depths and the weakness of the patient prohibited surgical intervention. She was discharged from the hospital seven months after the first consultation, without improvement. Since then the lesions have seemed to be stationary; for twenty months after the onset of the illness the local and general conditions have remained the same.

Histologic Examination.—The first and second biopsies showed similar pictures and may therefore be included in a single description.

The sections were composed of normal epidermis and subcutaneous tissue, which was rich in elastic fibers and presented an abundant cellular infiltration. There were many small and approximately round foci, which were partly fused

Fig. 1.—A composite granule embedded in an area of polymorphonuclears, which are in turn surrounded by lymphocytes, plasmocytes and histiocytic elements. Magnification, × 13.

together and formed some larger polycyclic areas. In the neighborhood were some smaller, often perivascular cellular nodules, sometimes surrounding the hair bulbs and the glands of the skin.

The center of almost every focus was formed by well preserved and living polymorphonuclears, which were surrounded by a large strip of lymphocytes and plasmocytes. Between the latter were threads of larger cells, which corresponded partly to collapsed capillaries or neocapillaries, not yet canalized, and partly to histiocytes. In a few foci were noted some granular or fibrillar fibrin and red cells in large or small numbers. The cellular constitution of this inflammatory infiltration did not, therefore, present any special character.

The majority of the nodules, however, contained peculiar elements in the central polymorphonuclear area, the first aspect of which suggested actinomycotic granules (fig. 1). They were composed of an anhistic cuticular membrane, partly

provided with minute clubs and encircling an anuclear mass, which was finely granular and sometimes subdivided by small and indefinite walls. The cuticulum was refractory and obviously hard, breaking under the microtome knife and sometimes even falling out of the sections during the cutting. It stained well with magenta red. It stained blue by the Dominici-Mann-Masson method and red by Masson's trichrome method. It remained strongly colored by the Ziehl-Kühne-Borrel method, much less by the ordinary Ziehl method. It stained moderately with the diluted Ziehl solution. With all these stainings the cuticulum looked relatively thick and homogeneous. The May-Grünwald-Giemsa and the Pappenheim stain decomposed it into a very thin external membrane, colored blue or grayish green, and an inner layer, colorless and relatively thicker, closely adjacent to the outer layer.

The outlines of the granules were sometimes round or oval and sometimes irregularly depressed; in a small number of granules the membrane was perfectly smooth, and in others, slightly rough; in most instances it was furnished with minute protuberances of different shapes, some of them being plain and like the clubs of actinomycotic granules (fig. 2*A*) and others being formed by minute polypoid hernias continuing directly from the principal membrane. In some rare instances there were finely notched asperities at the limit of visibility (fig. 2*A*, to the left).

The inner area of the granules was formed of a granular and in certain places filamentous substance (fig. 2*B*). The granulations were of various dimensions but remained within the limits presented by staphylococci of an old culture, sharing with them the staining properties. A large number were frankly gram-positive; others stained less or not at all. The latter were mostly large or indefinite granulations, resembling in all respects dying bacteria undergoing lysis. The gram-positive cocci generally filled the whole space, but in some granules there were also bacilliform, slender or thick, long or short elements which were gram-negative and which stained lightly blue by the Dominici-Mann-Masson method and red by the Pappenheim methyl green and pyronine method (fig. 2*B*). They seldom mingled with the cocci but occupied generally the peripheral space, separating the cocci from the membrane. The inner small dividing walls seen in some granules were made up of an apparently soft substance with indefinite staining properties.

In the neighborhood of the granules the exudate sometimes contained hollow, vesicular or irregularly folded structures (fig. 3*A*). Some were connected with the membranes of granules, but others were wholly independent. The walls were delicate but distinct and took the stain like the outer part of the thick cuticulum. Many of the cavities were empty; others contained cocci (fig. 3*B*), and a few contained some polymorphonuclear leukocytes.

Histologic Diagnosis.—The structure of the granules and of the surrounding inflammatory tissue was strongly characteristic of a botryomycotic lesion, if one disregards the bacilliform bacteria, the presence of which inside the granules was a new observation, which will be discussed later.

There were seen microbic clusters, partly subdivided, presenting all the morphologic features of staphylococci and surrounded by a cuticulum which was sometimes smooth and sometimes rough. The excrescences were at times of the shape and size of actinomycotic clubs, while sometimes they were less protruding and more minute or even consisted only of irregular thickenings of the membrane. Magrou has shown that the granules of spontaneous botryomycosis in the horse have a relatively simple cuticulum, deprived of typical clubs, whereas in the experimentally produced granules in the guinea-pig, clubs were regularly

seen. The granules in our case were therefore of an intermediate type, some being bare and others furnished with clubs.

Bacteriologic Examination.—The culture of the sample taken for the second biopsy yielded two microbes—a coccus and a bacillus. The first was identified as a typical, very chromogenic strain of Staphylococcus aureus. The bacillus was gram-negative; it did not liquefy gelatin; it produced indole in minute quantity; it fermented dextrose, levulose, lactose, maltose and mannose but not saccharose, and it blackened a medium of agar containing lead subacetate. The bacillus therefore belongs to the group of colon bacilli.

Comment.—These results correspond closely to the histologic observation that two bacteria were present in many granules. The similarity allows the conclusion that the gram-negative bacilli in the sections were most probably of the colon type. Their presence in the granules permits the exclusion of the hypothesis that the presence of the colon bacilli was due to an accidental pollution.

But the presence of colon bacilli was a unique fact in the history of botryomycosis. It is not very surprising to find a colon bacillus in an inflammatory lesion of the perineal region, but nevertheless the question arises whether in this instance the bacillus was playing an active rôle in the granule formation. This question can be approached only by discussing the pathogenesis of the botryomycotic lesions.

PATHOGENESIS

Magrou proved that the staphylococcus is able to produce botryomycotic granules without the help of any other parasitic agent. It is highly improbable for an associated microbe to have escaped the attention of as experienced a bacteriologist as Magrou. We stated before that according to him the formation of granules depends essentially on the number of germs injected. The quantity should be such that, on the one hand, the phagocytic activity of the organism does not succeed in completely eliminating the infection and that, on the other hand, the germs are unable to produce a severe necrosis. The ability of the clusters of staphylococci to surround themselves with a membrane and to multiply within its shelter depends on this equilibrium. It is clear that in Magrou's experiments the rôle played by the dose seemed to be dominant, because botryomycotic lesions were obtained at will after establishing this dose between certain limits.

However, one may ask whether in spontaneous botryomycosis the quantity of invading germs alone or other factors may intervene and control the formation of granules and clubs.

The castration fungus in the horse seems to appear too often, not to say too regularly, to be due to a definite number of invading germs. We cannot refrain from admitting in this case that the histologic substratum of the scrotal region plays a part in the botryomycotic evolution. In the

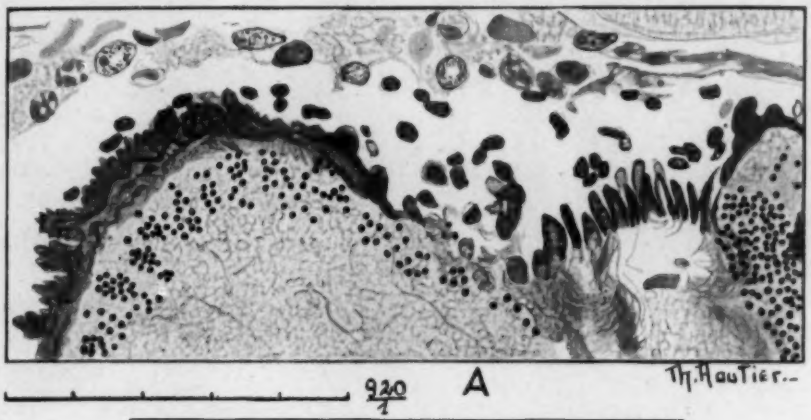

Fig. 2.—*A*, an old granule with club-garnished shell and staphylococci in the peripheral zone. (Stained by Gram's method, with diluted Ziehl counterstain). *B*, a young granule, showing a shell, which is still thin and ungarnished; colon bacilli, and staphylococci. (Pappenheim methyl green and pyronine stain).

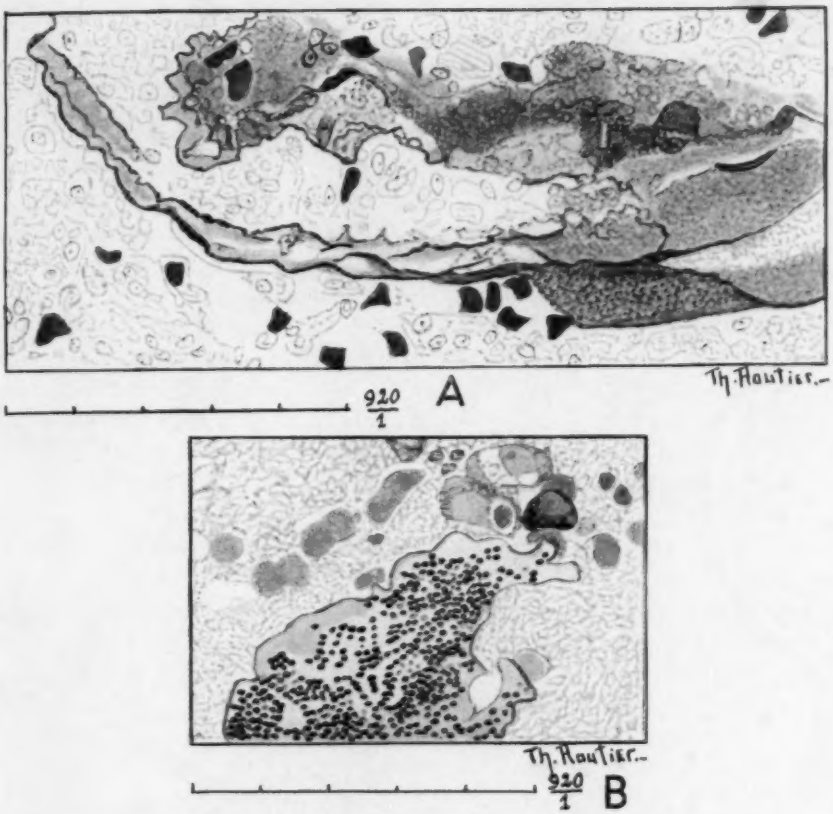

Fig. 3.—*A*, membranes of fibrin-like shape in the exudate (to the right they are shown cut tangentially). There are no organisms. (Giemsa stain.) *B*, a delicate and sinuous membrane surrounding young and vigorous staphylococci, constituting a beginning granule. (Giemsa stain.)

three or four cases in man reported previous to our own, botryomycosis was always limited to bones. In regard to the multitude of staphylococcic infections in the human being, this predominating localization is equally difficult to explain only by the number of infective agents and without admitting that the osseous substance plays a part. In our own case, the first case in which botryomycosis has been shown evolving in human soft tissue, conditions were peculiar, as the infection was a mixed one, the colon bacilli participating actively in the infectious process. In most staphylococcic infections there are at the beginning only a few microbes, but these progressively increase in number; the quantitative equilibrium necessary to botryomycotic transformation should therefore be attained, at least temporarily, more often than the reported incidence of botryomycosis.

For all these reasons, one is led to suspect that other factors intervene and to attribute to the tissues of the host a greater importance than Magrou seemed to do. It is true that in a footnote [14] in his paper he asked whether the zoogleic and amorphous substance which encircles the youngest colonies of microbes and precedes the appearance of the cuticulum "could not in part be due to a transformation of the collagenous substance secreted by the fibroblasts: these latter are very numerous in botryomycotic tumors, in the vicinity of the fibrous threads which delimit the foci; it is possible that a part of the secreted collagen, instead of organizing in fibers, degenerates under the action of the microbic toxins and is transformed into a semifluid material which could impregnate the zooglea of the bacterial colonies." This tissue factor plays an important rôle in Masson's explanation, which was accepted by Fumagalli, concerning the pathogenesis in their cases of osseous botryomycosis: the staphylococci proliferate first in the shelter of haversian channels, and their toxins produce a slowly progressing necrosis of the osseous matter, which eventually disappears. At that moment the colonies, which contain many dead germs, come in contact with the exudate surrounding the sequestrum and with the dead microbes, which, cemented together, form in the peripheral zone a dense shell-like layer. Masson's view explains better how the microbes may escape phagocytosis in the beginning of the process, but the explanation takes into account only osseous lesions. Nevertheless, the previous cases in man as well as the predominant scrotal localization in the horse seem to show that the number of germs is not the only factor favoring the formation of the botryomycotic granules. It appears that botryomycotic evolution depends more on a special modification of the exudate than on the intrinsic quantity of germs. The modified exudate, in turn, depends on the quantity and virulence of the germs. The fact that several factors

14. Magrou,[5] p. 35.

are necessary to provoke botryomycosis then explains the relative rarity of the disease.

In our own case anhistic membranous elements were observed in the exudate. These membranes resembled fibrin but did not show specific staining properties; some of them were empty, while others contained a more or less appreciable number of young and vigorous staphylococci, often in diplococcic arrangement, with no dead microbes present. The membranes seemed to result, at least in part, from a peculiar coagulation necrosis of small vascular or capillary walls or of elastic fibrils, which were abundant in the infected region. They appeared to be probably beginning shells, and the staphylococci seemed to find shelter in their sinuosities. It may be that later the shells thicken through internal apposition of protein material resulting from dead microbes. The pathogenesis in our own case would then be closely similar to that in osteomyelitic lesions, the membranes playing a rôle similar to that of the haversian channels.

The question arises as to whether in our case the colon bacilli should not have favored the formation of the granules. We cannot consider that their presence was fortuitous, because these bacilli participated in the inflammatory process and continued to proliferate when enclosed in the granules, as shown by their polymorphism and the presence of elongated forms. It is possible that they controlled to a certain extent the necrosis which produced the membranes, previously referred to, or that they secreted antiphagocytic substances, recently shown by Pike,[15] which may have aided in holding the polymorphonuclears away from the bacteria. They may also have lowered the strength of the staphylococci, which perhaps otherwise would have given rise to an abscess, by hampering their growth, as Régnier and Lambin [16] demonstrated recently in mixed cultures. Their exact rôle can be established only by experiments, which we intend to undertake at the earliest opportunity, but we think that in our case the colon bacilli participated in establishing between host and germs the equilibrium which Magrou showed to be necessary in order to produce botryomycosis. We thus readily accept this equilibrium hypothesis but do not limit its conditions to the quantity of germs.

COMMENT

The botryomycotic evolution in staphylococcic infection raises questions of foremost biologic importance. Granule formation and the appearance of clubs seemed for a long time to be the pathognomonic sign of actinomycotic lesions. The majority of authors considered the shells and clubs to be a peculiar, resistant form produced by the mycotic

15. Pike, R. M.: J. Immunol. **26**:69, 1934.

16. Régnier, J., and Lambin, S.: Compt. rend. Acad. d. sc. **199**:1682, 1934.

threads themselves and regularly appearing in the invaded tissues. Conforming to these views and by analogy, Magrou expressed the belief that in botryomycosis the presence of both elements—grains and clubs—is essentially the product of the zoogleic evolution of the staphylococci, attributing only a secondary influence to the exudate. But since the publication of Magrou's paper the ideas on actinomycosis have been changing. On the one hand, cases of actinomycotic infections have been reported in which granules were entirely lacking (Sartory and his associates,[17] Gammel [18]). On the other hand, it was long a matter of conjecture whether the actinomycotic clubs were encountered only in vivo and only exceptionally obtained in cultures grown in pleural exudate (Wright [19]). Protein substances seemed therefore to be necessary to club formation, and the clubs appeared to be the result of an interaction between the fungus or its toxins and the surrounding proteins, leading to a kind of coagulation or precipitation around the peripheral protruding mycotic threads. This view was particularly sponsored by K. Meyer,[20] M. Meyer, A. Sartory, R. Sartory and J. Meyer.[21] Thus, the homogeneous matter forming the actinomycotic clubs would in the last instance be essentially of extraparasitic origin. We do not think that the results obtained by Bayne-Jones [22] were contrary to the new interpretation and favored the theory "attributing to the clubs a developmental part in the life cycle of the organism." Indeed, on the one hand, K. Meyer [20] obtained clubs with dead actinomycotic filaments, and, on the other hand, the Bayne-Jones medium, although not enriched, nevertheless contained animal proteins in meat broth, and the fungus was further associated with Klinger's Bacterium actinomycetum-comitans, which formed another source of protein.

As early as 1902 Lignières and Spitz [23] described an epizootic disease of cattle in Argentine in which they observed actinomycotic-like granules surrounded by clubs but which was due to a true bacillus that never showed filaments. Lignières expressed the opinion that actinophytic transformation occurs not only in many fungi but even in some bacteria, for instance in tubercle bacilli (Babes and Levaditi [24]) and

17. Sartory, A.; Sartory, R.; Weill, J., and Meyer, J.: Bull. Acad. de méd., Paris **107**:597, 1932.

18. Gammel, J. A.: Arch. Dermat. & Syph. **29**:287, 1934.

19. Wright, J. H.: J. M. Research **13**:349, 1904-1905.

20. Meyer, K.: Compt. rend. Soc. de biol. **115**:1684, 1934.

21. Meyer, M.; Sartory, A.; Sartory, R., and Meyer, J.: Presse méd. **43**:568, 1935.

22. Bayne-Jones, S.: J. Bact. **10**:569, 1925.

23. Lignières, J., and Spitz, G.: Arch. de parasitol. **7**:428, 1903; Bull. Acad. de méd., Paris **49**:125, 1903.

24. Babes, V., and Levaditi, C.: Compt. rend. Acad. d. sc. **124**:791, 1897; Arch. de méd. expér. **9**:104, 1902.

the actinobacillus recently discovered by them. It appears today that this opinion was prophetic. Since Magrou showed actinophytic evolution to appear in staphylococcic infection, analogous structures have been obtained not only with dead tubercle bacilli (K. Meyer and E. Mayer [25]) but even in granulomas produced by an inorganic substance, such as tellurium (Levaditi and Dimancesco-Nicolau [26]). The club formation and, in part, the shell formation appear therefore to be not only, as Lignières and Spitz and Magrou said, a fairly widespread attribute of different kinds of microbes but even more a general biologic reaction modality of inflamed tissues, a modality which may be determined partly by the nature and the quantity of the pathogenic agent. One may conceive that in some fungi the actinophytic property will more easily manifest itself, whereas in bacterial infections it presupposes the existence of peculiarly favorable conditions.

Our own case tends to confirm this conception, for we were led to consider the shells and clubs of botryomycotic granules to be essentially, at least in the beginning, of extrabacterial origin and to proceed either from seminecrotic exudative elements or from some protein substance precipitated in the exudate as a result of the presence of the germs or under the influence of their metabolic or toxic secretions.

NOMENCLATURE

The term botryomycosis is ambiguous and misleading. By its etymology and its application since the publication of the article by Rivolta, not only does it imply that the lesion is mycotic, but through the erroneous extension by Poncet and Dor it has been widely misused. Since the staphylococcic nature of these lesions was proved by Magrou's experiments and since others have identified various other staphylococcic lesions in animals and in man with the original botryomycosis, one may ask whether the substitution of a more appropriate term is not advisable. We are in favor of such a change in nomenclature, particularly since only five cases (including our own) have thus far been reported in man. This is therefore a most favorable opportunity to put an end to the perpetuation of an erroneous conception.

We showed that the formation of granules, shells or clubs is a characteristic that does not belong exclusively to fungi, as was long thought, but may be seen also in infections due to other organisms, of which the staphylococcus is only one example. In other words, actinophytic evolution, though generally present in streptotrichal actino-

25. Meyer, K., and Mayer, E.: Ztschr. f. Hyg. u. Infektionskr. **108**:38, 1927; quoted by Meyer and others.[20]

26. Levaditi, C., and Dimancesco-Nicolau, O.: Compt. rend. Soc. de biol. **95**: 531, 1926.

mycosis, may appear also in bacterial infections. Lignières and Spitz proposed calling the granuloma due to their actinobacillus *Actinophytose à actinobacilles* (actinobacillar actinophytosis), in comparison with *actinophytose à streptothrix* (streptotrichal actinophytosis), which comprises the classic and truly fungous actinomycosis. This proposition may easily be extended to botryomycosis by calling it staphylococcic actinophytosis. Lignières' nomenclature may be applied further to all mycotic and bacterial granulomas in which grain formation with clubs may occur.

We therefore propose to replace, at least in human pathology, the word botryomycosis by the name staphylococcic actinophytosis.

SUMMARY AND CONCLUSIONS

A case of true genital botryomycosis in a woman is recorded. It is the fifth case in man to be reported in the literature and the first to be observed in soft tissues, all others having been encountered in chronically osteomyelitic bone. The lesions were inflammatory and contained granules resembling those seen in actinomycosis but formed by clusters of staphylococci, which were sometimes associated with colon bacilli. The granules were lined by shells, partly garnished with clubs.

The lesions were identical with those described in animals, particularly in the horse, under the name of botryomycosis, the nature of which was proved by Magrou's fundamental work to be staphylococcic. In our case the coexistence of colon bacilli inside the granules constituted a heretofore unknown feature. The eventual participation of these bacilli in the granule formation is discussed. Opportunity is taken to refute the identification of true botryomycosis with telangiectatic or pedunculated granuloma or hyperplastic angioma in man.

A survey is made of infections showing actinophytic evolution. This appears to be a biologic reaction modality of the organism and to be more frequent than is suspected. It is not restrained to fungus infections but may appear also in actinobacillosis, in staphylococcic infection and in tuberculosis. In accordance with Lignières, who called his actinobacillosis actinobacillar actinophytosis, we propose to replace the name botryomycosis with staphylococcic actinophytosis. This substitution of a new designation is justified by the fact that the name botryomycosis is very misleading and only a few cases of staphylococcic actinophytosis in man have thus far been reported.

The combined analysis of the histogenesis in our own case and of the cases reported in the literature seems to indicate that the granules, shells and clubs are not a direct result or product of the pathogenic agent but seem to arise through a peculiar interaction between these agents and the surrounding exudative elements.

REACTIVITY OF MALIGNANT NEOPLASMS TO BACTERIAL FILTRATES

I. THE EFFECT OF SPONTANEOUS AND INDUCED INFECTIONS ON THE GROWTH OF MOUSE SARCOMA 180

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It has recently been observed that bacterial factors capable of eliciting the phenomenon of local cutaneous reactivity to bacterial filtrates also produce on intravenous injection selective hemorrhagic necrosis in liposarcoma of guinea-pigs (Gratia and Linz [1]), sarcoma 180 of mice (Shwartzman and Michailovsky [2]), $\frac{S}{37}$ sarcoma, $\frac{M}{63}$ adenocarcinoma, Twort adenocarcinoma of mice (Duran-Reynals [3]) and Ehrlich adenocarcinoma of mice (Apitz [4]). No hemorrhagic lesions are produced in spontaneous or transplantable slow-growing malignant tumors, malignant tumors rapidly growing in heterologous hosts, embryomas and granulomas (Duran-Reynals [3]).

The work described in this paper deals with the effect of spontaneous and induced infections on the development of mouse sarcoma 180.

The tumor employed was mouse sarcoma 180 of the Crocker Institute for Cancer Research. The mortality of inoculated mice within the first month is approximately 45 per cent. Few mice live longer than six weeks. Spontaneous cure takes place in a small number. In spite of the high degree of malignancy of the tumor, no metastases are observed, probably because of the short span of life of mice that have been inoculated. The average diameter of the tumors is 1 cm. by the end of the second week. No fluctuations in the growth energy and no seasonal influences on the growth of the tumor have been observed. The tumor "takes" in 100 per cent of heterogenous lines of mice.

EFFECT OF SPONTANEOUS INFECTIONS ON DEVELOPMENT OF MOUSE SARCOMA 180

A mouse bearing a fourteen day old sarcoma 180 was obtained on Sept. 28, 1934, from the Crocker Institute for Cancer Research (Crocker generation 377 B).

From the Laboratories of the Mount Sinai Hospital.

This investigation has been aided by a grant from the Josiah Macy Jr. Foundation.

1. Gratia, A., and Linz, R.: Compt. rend. Soc. de biol. **108**:427, 1931.

2. Shwartzman, G., and Michailovsky, N.: Proc. Soc. Exper. Biol. & Med. **29**:737, 1932.

3. Duran-Reynals, F.: Proc. Soc. Exper. Biol. & Med. **31**:341, 1933.

4. Apitz, K.: Ztschr. f. Krebsforsch. **40**:50, 1933.

The tumor was maintained by bimonthly passages through a heterogenous stock of mice.

The transplants were made by means of a trocar inserted into the subcutaneous tissues. The inoculum was deposited at a distance not less than 1 inch (2.5 cm.) from the point of insertion of the trocar. Firm and healthy pieces of from twelve to fourteen day old tumors were selected for transplantation. Tracings of tumor growth and records of the appearance of the tumor were made two or three times a week, beginning with the twelfth day following inoculation. In the experiments to be described tumors measuring 1 by 1 cm., 1 by 1.5 cm. and 1.5 by 2 cm. are referred to as 1+, 2+ and 3+ tumors, respectively. Tumors measuring 2 by 2 cm. and larger ones are referred to as 4+ tumors.

In the following pages are the data on the appearance of the tumors, the mortality of the tumor-bearing mice and the bacteriologic studies on stock and tumor-bearing mice for a period of four and one-half months.

Passage on Oct. 12, 1934 (Crocker Generation 377 B).—Thirty-six mice were inoculated. None died within the first two weeks. Tumors developed in all the mice. The appearance and size of the tumors in 20 mice were recorded twelve days after inoculation. Of these, 16 showed growth 4+ and 4 showed growth 2+. Small central hemorrhages were observed in the tumors of 3 mice.

Passage on Oct. 26, 1934 (Crocker Generation 377 B).—Sixty mice were inoculated. Three died within the following twelve days. Tumors developed in all the surviving mice. A record of the size of the tumors in 47 mice disclosed growth 3+ in 20 and growth 2+ in 27 twelve days after inoculation. No spontaneous hemorrhages were seen.

Passage on Nov. 9, 1934 (Crocker Generation 377 B).—Sixty mice were inoculated. Six died during the following twelve days. Tumors developed in all the surviving mice. Of 34 mice examined twelve days after inoculation, 17 showed growth 4+ and 17 showed growth 2+. Small central hemorrhages were noticed in the tumor in 2 mice.

Passage on Nov. 15, 1934 (Crocker Generation 377 B).—One hundred and eleven mice were inoculated. Ten mice died within the following twelve days. Tumors developed in all the surviving mice. The appearance and size of the tumors were recorded in 69 mice twelve days after inoculation. Twenty-four mice showed growth 3+ and 45 showed growth 2+. No spontaneous hemorrhages were noted.

Passage on Nov. 30, 1934 (Crocker Generation 377 B).—Seventy mice were inoculated. Two mice died within the following two weeks. Tumors developed in all the surviving mice. The appearance and size of the tumors were recorded for 31 mice twelve days after inoculation. Twenty mice showed growth 3+ and 11 showed growth 1+. Small central hemorrhages were observed in the tumors of 5 mice.

Passage on Dec. 28, 1934 (Crocker Generation 377 B).—Seventy mice were inoculated. Eight died within the following twelve days. Thirteen failed to show tumors. Tumors of 2 mice regressed spontaneously within three weeks after inoculation. The remaining 49 mice showed growth 1+ twelve days after innoculation.

Passage on Jan. 4, 1935 (Crocker Generation 377 B).—One hundred mice were inoculated. Forty-five died within the following twelve days. Twenty-eight showed no tumors, and in 27 tiny necrotic tumors developed.

Passage on Jan. 11, 1935 (Crocker Generation 377 B).—One hundred mice were inoculated. Twenty-five died within the following twelve days. Two weeks after transplantation the remaining 75 mice showed growth 1+. Spontaneous hemorrhages were noticed in the tumors of 6 mice. Ten mice kept for further observation died from twelve to twenty-nine days after inoculation. The 4 mice which survived for the longest period showed spontaneous hemorrhages and complete regression of the tumors.

Passage on Jan. 25, 1935 (Crocker Generation 377 B).—One hundred mice were inoculated. The results of this inoculation are summarized in table 1.

Comment.—Because of the unusually high mortality and the number of spontaneous regressions in the last three passages, bacteriologic examinations of material from the tumor-bearing mice were made in the following passages. The results of these studies are summarized in table 2.

As is seen, cultures of material from 5 mice of the passage of Jan. 25, 1935, made twelve days after tumor transplantation disclosed

TABLE 1.—*Data on Sarcoma 180 in Mice Spontaneously Infected with B. Enteritidis* *

Number of Days After Inoculation	Number of Dead Mice	Number of Examined Surviving Mice	Number of Surviving Mice Showing Following Tumors		
			Tumors with 1+ Growth	Tiny Necrotic Tumors	No Tumors
12	22	78	0	41	37
12-14	15	39	1	25	13
15-21	15	11	2	6	3
22-26	4	7	1	3	3
27-34	7	0	..	..	..

* This passage was made on Jan. 25, 1935. The readings of the size of the tumors recorded in this table were made from seven to fifty-four days after inoculation. Some of the mice not recorded in this table were used in additional experiments.

Enterococcus and Bacillus enteritidis in the tumor tissue, peritoneal and pleural fluids, liver and heart blood.

The diagnosis of enterococcic infection was confirmed by esculin fermentation and heat resistance tests, and that of B. enteritidis infection, by comparative agglutination tests with immune serums of Bacillus paratyphosus A, Bacillus paratyphosus B, Bacillus Morgani, B. enteritidis and Bacillus aertrycke.

Passage on Feb. 1, 1935 (Crocker Generation 377 B).—Ten mice were inoculated. Twelve days after inoculation 7 showed growth 2+ and 3 showed growth 1+. Central hemorrhages developed in four tumors of this set. Within thirty-two days after inoculation 5 mice died. Three showed complete regression of the tumors, and 2 showed tiny necrotic tumors with central hemorrhages.

Passage on Feb. 8, 1935 (Crocker Generation 377 B).—A group of 15 mice were inoculated. During the following twelve days 1 mouse died and 5 mice failed to show any growth. The remaining mice showed tiny necrotic tumors. Six of these died within thirty-one days after inoculation. At this time there were observed spontaneous regressions of tumors in 3 and tiny necrotic tumors with central hemorrhages in the remaining mice.

B. enteritidis, Staphylococcus and Fridländer's bacillus were recovered from regressing tumors and organs of 3 mice examined seventeen days after inoculation.

TABLE 2.—*Bacteriologic Findings in Mice Infected with B. Enteritidis*

Date of Tumor Passage	Appearance and Size of Tumor	Date of Examination	Bacteriologic Examinations					Number of Mice Examined
			Tumor	Peritoneal Fluid	Pleural Fluid	Heart Blood	Liver	
1/25/35	Tiny, necrotic	2/ 6/35	Enterococcus and B. enteritidis	B. enteritidis	Negative	Negative	Enterococcus and B. enteritidis	1
1/25/35	Tiny, necrotic	2/ 6/35	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	Enterococcus, B. enteritidis and diphtheroids	1
1/25/35	Growth 1+; hemorrhagic in center	2/ 6/35	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	Enterococcus and B. enteritidis	1
1/25/35	Tiny, necrotic	2/ 6/35	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	Enterococcus and B. enteritidis	1
1/25/35	No tumor	2/ 6/35	B. enteritidis	B. enteritidis	B. enteritidis and enterococcus	Enterococcus	B. enteritidis	1
2/ 8/35	Spontaneous regression	2/25/35	B. coli, enterococcus, B. Friedländeri and Staph. aureus	Staph. aureus, B. Friedländeri and B. enteritidis	B. enteritidis, Staph. aureus, B. Friedländeri	B. enteritidis and Staph. aureus	B. enteritidis and B. Friedländeri	1
2/ 8/35	Spontaneous regression	2/25/35	Staph. aureus and B. enteritidis	Negative	Negative	Negative	B. enteritidis and Staph. aureus	1
2/ 8/35	Spontaneous regression	2/25/35	Staph. aureus	Staph. aureus	Staph. aureus	B. enteritidis	B. enteritidis	1
2/15/35	Small; no hemorrhage	2/27/35	Negative	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	1
2/15/35	Tiny, necrotic	2/27/35	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	1
2/23/35	Small; no hemorrhage	3/ 7/35	Negative	Negative	Negative	Negative	Negative	1
2/23/35	Hemorrhage 3+; growth 1+	3/ 7/35	B. enteritidis	B. enteritidis	Negative	Negative	B. enteritidis	1
2/23/35	Hemorrhage 3+; growth 1+	3/ 7/35	B. enteritidis and enterococcus	Enterococcus	Negative	Negative	Negative	1
2/23/35	Small; no hemorrhage	3/ 7/35	Negative	Negative	Negative	Negative	Negative	1
2/23/35	Small; no hemorrhage	3/ 7/35	Negative	Negative	Negative	Negative	Negative	1
3/ 1/35	Small; no hemorrhage	3/ 6/35	Negative	Negative	Negative	Negative	Negative	1
3/ 1/35	Small; no hemorrhage	3/ 6/35	Negative	Negative	Negative	Negative	Negative	1
3/ 1/35	No tumor	3/ 6/35	Negative	Negative	Negative	Negative	Negative	1
3/ 1/35	Small; no hemorrhage	3/ 9/35	Negative	Negative	Negative	Negative	Negative	3
3/ 1/35	Small; no hemorrhage	3/13/35	Negative	Negative	Negative	Negative	Negative	1
3/ 1/35	Small; hemorrhagic center	3/13/35	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	2
3/ 1/35	Small; hemorrhagic	3/13/35	Negative	Negative	Negative	Negative	Negative	1
3/ 8/35	Small; hemorrhagic center	3/20/35	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	1
3/ 8/35	Hemorrhagic scar	3/20/35	B. enteritidis	B. enteritidis and Str. gamma	B. enteritidis	B. enteritidis	B. enteritidis	1
3/ 8/35	Hemorrhage 2+	3/20/35	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	B. enteritidis	3
3/22/35	Growth 3+; no hemorrhage	3/ 8/35	Negative	Negative	Negative	Negative	Negative	1
3/22/35	Growth 2+; doubtful central hemorrhage	4/15/35	Negative	Negative	Negative	Negative	Negative	6

Passage on Feb. 15, 1935 (Crocker Generation 377 B).— One hundred mice were inoculated. Eleven mice died during the following twelve days. Twelve days after inoculation 15 mice were selected at random as a control group. At that time 8 of these showed growth 2+ and 7 showed tiny necrotic tumors. Ten mice died from fifteen to twenty-four days after inoculation. Two showed growth 2+, and 3 showed no tumors. Material from the tumor of 1 and the organs of 2 mice cultured twelve days after inoculation of the mice revealed B. enteritidis.

Passage on Feb. 22, 1935 (Crocker Generation 377 B).—Mice of this passage were used for different experiments shortly after inoculation. For this reason the mortality rate could not be estimated. Twelve days after inoculation 4 of the 15 surviving mice showed no tumors, 4 showed tiny necrotic tumors and 7 showed growth 1+. Material from organs and the tumors of 5 mice was cultured at that time. B. enteritidis was recovered from the tumors of 2 mice and the organs of 1 mouse. Enterococcus was recovered from the tumors and organs of 1 of these 2 mice. Cultures of material from 3 mice were sterile.

TABLE 3.—*Data on Sarcoma 180 in Mice Spontaneously Infected with B. Enteritidis* *

Number of Days After Tumor Inoculation	Number of Dead Mice	Number of Dead Mice Showing			Number of Examined Surviving Mice	Number of Surviving Mice Showing		
		Tumors with 1+ Growth	Tiny Necrotic Tumors	No Tumors		Tumors with 1+ Growth	Tiny Necrotic Tumors	No Tumors
11	43	0	4	0	53	24	29	0
12-14	12	0	12	0	32	13	19	0
15-17	3	0	0	0	22	10	12	0
18-19	2	0	2	0	20	7	12	1
20-23	6	0	3	3	14	7	4	3
24-26	4	0	0	3	5	3	1	1
27-43	5	1	0	4	0	0	0	0

* This passage was made on March 8, 1935. The readings of the sizes of the tumors recorded in this table were made from seven to fifty-four days after inoculation. Some of the mice not recorded in this table were used in additional experiments.

Passage on March 8, 1935 (Crocker Generation 377 B).—One hundred mice were inoculated. The results of this inoculation are summarized in table 3. B. enteritidis was recovered from the tumors and organs of 5 mice examined twelve days after inoculation.

Passage on March 8, 1935 (Crocker Generation 389 A).—Material from the two week old tumor of a mouse obtained from the Crocker Institute was inoculated into a group of mice. Cultures of material from the organs and tumor tissue of the Crocker Institute mouse were sterile. Within the following twelve days 1 of the mice died and the others showed growth 2+. Two tumors (A and B) in good condition were selected for further passages. Repeated cultures of heart blood, peritoneal and pleural fluids and liver of a stock of mice obtained from a new dealer were sterile.

Passage on March 22, 1935, Series I (Crocker Generation 389 A).—Thirty mice were inoculated with tumor A. A culture of inoculum A showed B. enteritidis. None of the mice died during the following twelve days. The size and appearance of the tumors of 21 mice were recorded two weeks after inoculation. Nine mice showed growth 3+, and 12 showed growth 1+. One month after inoculation regressions were observed in 3 mice, the remaining mice showing normally developed tumors. Repeated cultures of material from mice killed at frequent intervals were sterile.

Passage on March 22, 1935, Series II (Crocker Generation 389 A).—Seventy mice were inoculated with material from tumor B. Cultures of material from this tumor were sterile. One of the mice died within the following two weeks. The size and appearance of the tumors were recorded for 58 mice. There were growth 1+ in 19, growth 2+ in 16 and growths 3+ and 4+ in the remaining mice.

Passage on April 3, 1935 (Crocker Generation 389 A).— One hundred mice were inoculated. Culture of material from the twelve day old tumor used for transplantation was sterile. Three of the mice died during the two weeks following inoculation. The size and appearance of the tumors were recorded for 54 mice two weeks after inoculation. Twenty showed growth 1+ and 34 showed growth 3+. Small central hemorrhages were observed in the tumors of 8 mice.

Comment.—In the analysis of observations thus far recorded one is impressed by the sudden rise in the mortality rate during the initial twelve days following inoculation. It becomes possible, therefore, to group the various passages according to the normal mortality rate and a rate considerably above normal expectancy during this initial period, as follows:

Group 1 includes tumor passages made from Sept. 28 to Nov. 30, 1934, in 314 stock mice that were free from spontaneous infection. During the first twelve days there was a mortality rate of 6.7 per cent. Twelve days after inoculation the 202 surviving mice were examined.

Group 2 includes passages made from Dec. 8, 1934, to March 8, 1935, in 610 mice infected with B. enteritidis. During the first twelve days there was a mortality rate of 25.4 per cent. The size and appearance of the tumors twelve days after inoculation were recorded for 377 mice.

Group 3 includes passages made from March 8 to April 3, 1935, in 200 mice that were free from infection. Two per cent of these mice died during the first twelve days. The size and appearance of the tumors twelve days after inoculation were recorded for 133 mice. The incidence of "takes," tiny necrotic tumors, average-sized growths and large tumors is recorded in the accompanying chart (fig. 1).

Unfortunately, no bacteriologic examinations were made of the first three passages, for which there was a high mortality rate. Subsequent consistent bacteriologic findings, however, brought ample proof that the high rate was due to a spontaneous epidemic of B. enteritidis.

Spontaneous infection with B. enteritidis exerted a profound influence on the development of sarcoma 180, the number of "takes" being reduced by approximately 23 per cent. This is significant in view of the fact that under normal conditions the inoculations rarely failed to "take" provided the precaution of selecting firm and healthy, approximately twelve to fourteen day old tumor tissue was observed. The

tumors attained the average size in the usual percentage of mice two weeks after inoculation. However, the growth energy of tumors in the infected mice was apparently considerably reduced, as they did not show the 3 + and 4 + tumors observed in approximately 50 per cent of the noninfected mice at that period. One is also impressed by the high incidence of tiny necrotic tumors. Histologic section of a twelve day old tumor of this type (fig. 2) showed a pronounced hemorrhage, necrosis of tumor cells and thrombosis. Whenever mice showing necrotic

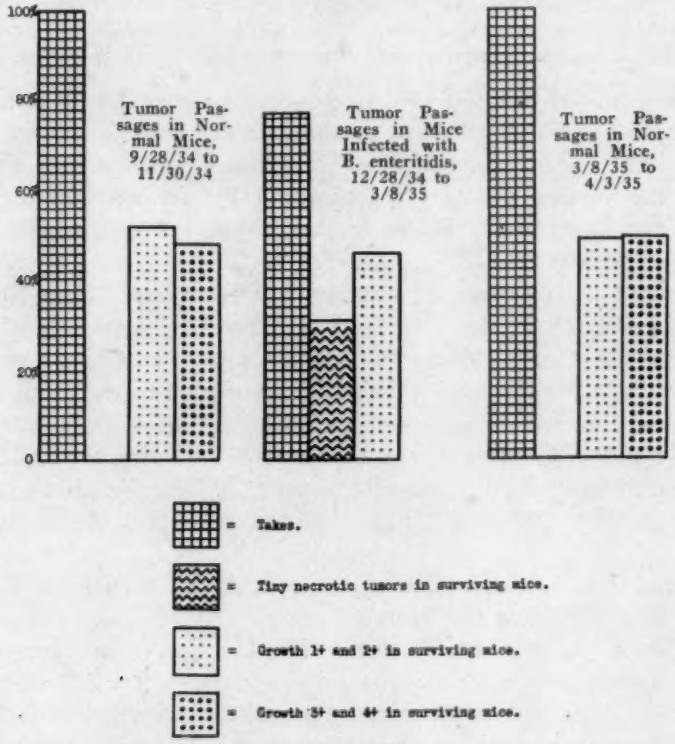

Fig. 1.—Chart showing the effect of spontaneous epidemics on the growth of mouse sarcoma 180.

tumors survived for a prolonged period, complete healing eventually took place. It may be safely stated that the incidence of spontaneous regression observed was far beyond normal expectancy. No definite conclusion may be drawn, however, concerning the percentage of regressions, since most of the infected mice died within the first month. The possibility still remains that the tumors might have resumed their growth if the mice had lived longer.

The passages of the tumor of Crocker generation 389 A also are of interest. As is seen, a group of 30 mice were inoculated with material from a tumor infected with B. enteritidis, and a group of 70 mice free from infection with B. enteritidis were inoculated with material from a sterile tumor. The tumors developed normally in both groups of mice. It appears, therefore, that the infection of the inoculum itself plays no rôle in the development and growth energy of the tumor provided the mice inoculated are either free from or immune to the infection.

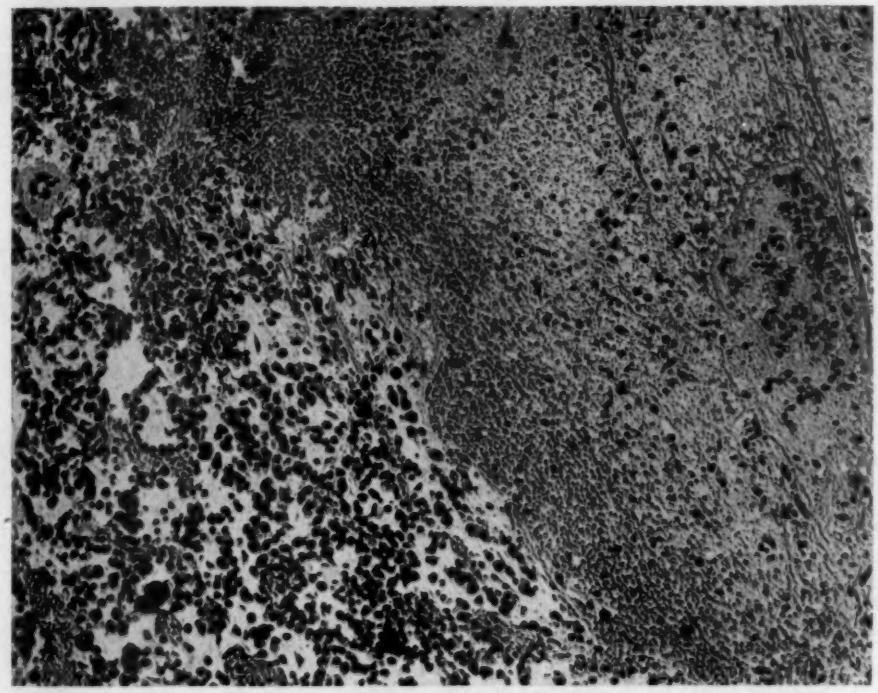

Fig. 2.—Section of twelve day old tiny necrotic tumor in a mouse with spontaneous infection of B. enteritidis. Note the evidence of severe hemorrhage and necrosis of the tumor. × 220.

Also, there seems to exist a certain correlation between the appearance of the tumor in a given infected mouse and the bacteriologic findings.

As shown in table 2, twelve days after inoculation tiny necrotic, spontaneously regressing and small hemorrhagic tumors were seen in mice infected with B. enteritidis. Small but nonhemorrhagic twelve day old tumors were observed in noninfected mice. To this a single exception was noted, the cultures in this instance being sterile—1 mouse had a small hemorrhagic tumor.

EFFECT OF INDUCED INFECTIONS ON DEVELOPMENT OF MOUSE SARCOMA 180

In these experiments live cultures and culture filtrates of B. enteritidis and Staphylococcus aureus were employed.

B. enteritidis was isolated from the heart blood of a tumor-bearing mouse of the passage made on Jan. 25, 1935 (Crocker generation 377 B). Every second and later every third day the strain was passed through plain broth containing B. enteritidis rabbit serum in 1:10 dilution. After nineteen passages a rough colony which self-agglutinated in plain broth and in an 0.85 per cent solution of sodium chloride was tested for virulence in normal mice (strain rough 3H). Three stock mice were inoculated with undiluted twenty-four hour old broth culture and 1:10, 1:50 and 1:100 dilutions thereof. The observations were made for a period of five days. While most of the mice inoculated with undiluted broth culture and broth culture diluted 1:10 died during the first three days, dilutions 1:50 and 1:100, with 2 exceptions, failed to kill the mice tested. Staph. aureus (6H) was isolated from the heart blood of a tumor-bearing mouse.

The B. enteritidis filtrate (T.1990) was an "agar washings" filtrate. The Staph. aureus filtrate was a filtrate of a three day old plain broth culture. Both filtrates were tested for their ability to elicit in rabbits the phenomenon of local cutaneous reactivity to bacterial filtrates. The B. enteritidis filtrate contained 500 reacting units. Staph. aureus produced no effect even in a dose of 3 cc. per kilogram of body weight. The results obtained with these strains and their filtrates in tumor-bearing mice are summarized in table 4. As is seen from this table, broth cultures of Staph. aureus and culture filtrates of Staph. aureus exerted no influence on the development of sarcoma 180.

An eighteen hour culture of the rough strain of B. enteritidis diluted 1:100 was injected intravenously into 20 mice bearing twelve day old tumors. Severe hemorrhagic lesions were observed in 11 mice, and mild hemorrhagic lesions, in 4 mice, twenty-four hours after the intravenous injection. Seven of these tumors completely regressed within ten days after the injection. Of the 3 mice that were alive twenty days after the injection 1 had no tumor, 1 showed a tiny necrotic tumor and 1 had an actively growing tumor.

Ten days after inoculation with the rough strain of B. enteritidis 2 mice were killed for bacteriologic examination. B. enteritidis was isolated from the tumor tissue, heart blood, peritoneal and pleural fluids and liver of both mice. The strain apparently was the same as the one injected, since it formed distinctly rough colonies on plain agar and gave spontaneous agglutination in plain broth and in an 0.85 per cent solution of sodium chloride.

Histologically the hemorrhagic tumor sectioned twenty-four hours after the injection of B. enteritidis (fig. 3) showed a zone of necrosis and hemorrhage sharply demarcating the viable tumor tissue. The "agar washings" filtrate (T.1990) of B. enteritidis injected intravenously in a dose of 1 cc. into mice bearing twelve day old tumors produced severe hemorrhagic lesions in 8 mice (fig. 4) and no effect in 2.

Comment.—As is seen from the foregoing observations, infections induced with B. enteritidis and injections of culture filtrates of B. enteritidis exert a strong inhibitory influence on the development of sarcoma 180. Infections with Staph. aureus and injections of culture filtrates of Staph. aureus produce no effect on the development of this

TABLE 4.—*Data Showing the Effect of Induced Infections on Mouse Sarcoma 180* *

Number of Mice	Appearance of Tumor Prior to Treatment	Material Used for Injection	Dose and Route of Injection	Occurrence of Death, Days				Effect Noted After Stated Period			Survivors	
				Immediate	1-2	3-10	11-20	1-2 Days	3-10 Days	11-20 Days	No.	Effect
10	Gr. +/6, ++/4	B. enteritidis filtrate (T.1990)	I.V. 1 cc.	0	10	0	0	Hem. +++/6, ++++/2	—	—	0	—
5	Gr. +++/4, ++/1	B. enteritidis filtrate (T.1990)	I.P. 1 cc.	0	5	0	0	Hem. ++++/2, +++/3	—	—	0	—
4	Gr. +/4	B. enteritidis filtrate (T.1990)	I.P. 1 cc.; Dil. 1:4	0	2	0	0	—	—	—	2	Regr. ++++/2
5	Gr. ++/4, +/1	B. enteritidis filtrate (T.1990)	I.P. 1 cc.; Dil. 1:4	0	2	1	0	Hem. ++++/4	Regr. ++++/2	—	2	Regr. ++++/2
7	Gr. +/4, ++/3	Staph. aureus (6 H), 18 hour broth culture	I.V. 1 cc.; Dil. 1:10	0	2	4	1	Hem. +/1	Gr. ++/3, +/2	Gr. +++/1	0	—
7	Gr. +/4, ++/3	Staph. aureus culture filtrate	I.V. 1 cc.	1	0	1	0	No effect	No effect	—	5	Gr. ++++/2, +++/1, ++/2
20	Gr. +/7, ++/3, ++/10,	18 hour culture B. enteritidis (rough 3 H)	I.V. 1 cc.; Dil. 1:100	0	0	14	3	Hem. ++++/11, ++/4	Regr. ++++/7	—	3	Tiny necrotic tumor in 1; Regr. ++++/1, Gr. +++/1

* Hem. indicates hemorrhage; Regr., regressions; Gr., growth; I.V., intravenously; I.P., intraperitoneally, and Dil., dilution. In the fractions the numerator indicates the degree, and the denominator, the number of mice.

Fig. 3.—Histologic appearance of a twelve day old tumor twenty-four hours after the intravenous injection of a live culture of rough B. enteritidis. The viable tumor tissue is sharply demarcated by the zone of hemorrhage and necrosis. × 220.

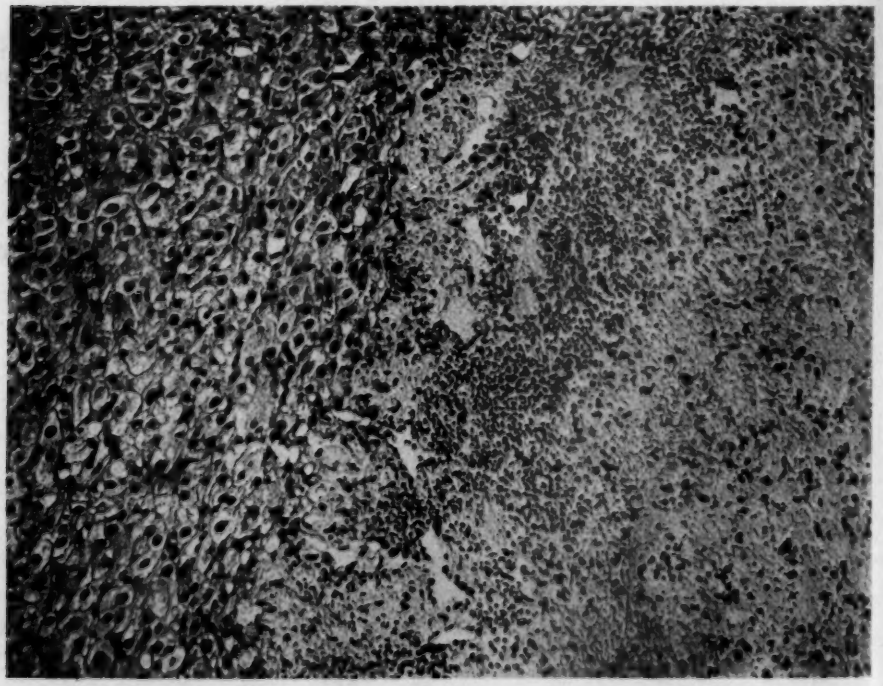

Fig. 4.—Section of a twelve day old tumor twenty-four hours after the intravenous injection of 1 cc. of a B. enteritidis filtrate (T.1990). The viable tumor tissue is sharply demarcated by a zone of hemorrhage and necrosis. × 220.

tumor. As will be remembered also, the filtrates of B. enteritidis are capable of eliciting the phenomenon of local cutaneous reactivity in rabbits in high dilutions, while the culture filtrates of Staphylococcus aureus produce no effect.

It is suggestive, therefore, that the inhibitory influence of an infecting micro-organism on sarcoma 180 is conditioned by its ability to secrete the factors necessary for the elicitation of the phenomenon of local cutaneous reactivity to bacterial filtrates in rabbits.

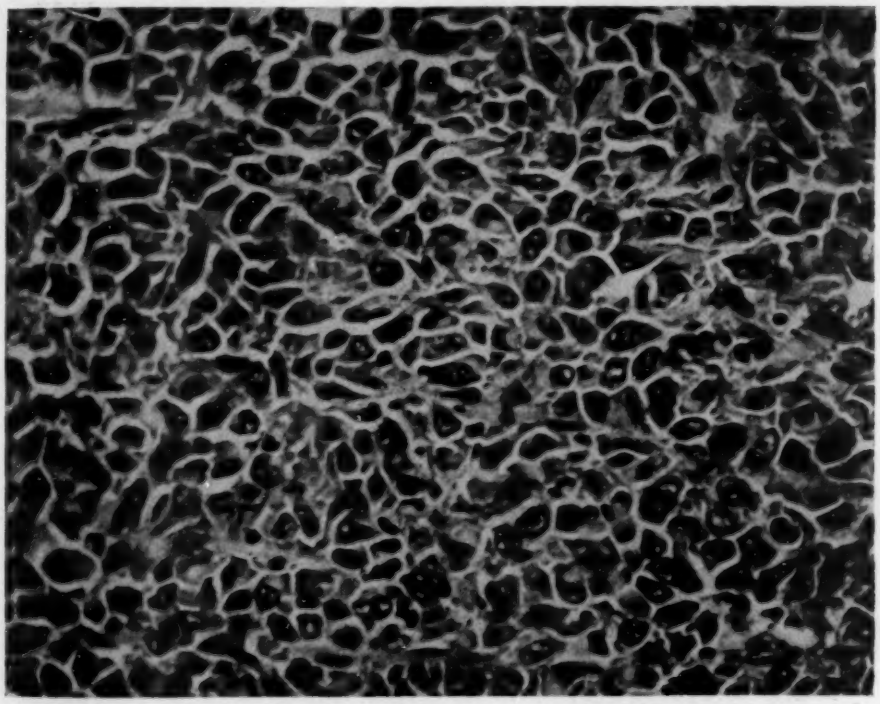

Fig. 5.—Histologic appearance of a normal twelve day old sarcoma 180. A high power view showing the immaturity of the cells and the numerous mitoses. × 460.

COMMENT AND CONCLUSIONS

As stated by Woglom,[5] it is a well known fact that transplantable tumors grow poorly in animals that are not in good health. The inhibitory effect of infections induced with trypanosomes, spirochetes, Bacillus tuberculosis, Bacillus bulgaricus-thermophilicus and Bacillus anthracis on the development of transplanted mouse and rat tumors was previously

5. Woglom, W. H.: Cancer Rev. 4:129, 1929.

reported by Daels,[6] Comsia,[7] Karczag, Csaba and Németh,[8] Roskin and Exempliarskaia,[9] Centanni and Rezzesi [10] and Boccolari-Segolini.[11] Other micro-organisms apparently produce no effect on tar carcinomas and transplantable tumors, i. e., Bang's bacillus, swine erysipelas, Streptococcus equinus adenitis (Boccolari-Segolini [11]), Sporotrichum Beurmanni (Lazzarini [12]), Spirochaeta pallida (Castiglioni [13]) and proteolytic gram-positive anaerobes (Torrey and Kahn [14]).

The work described in this paper demonstrates that spontaneous infection with B. enteritidis exerts a profound influence on the development of sarcoma 180. The percentage of "takes" and the growth energy are appreciably reduced. The tumors may become hemorrhagic and necrotic. Spontaneous regressions by far exceed the normal expectancy. It is also significant that infection induced with a comparatively avirulent rough strain of B. enteritidis produces a similar antagonistic effect on the development of the tumor. On the other hand, infection with Staph. aureus does not influence the development of the tumor.

As pointed out before, certain bacterial filtrates, namely, those capable of eliciting in rabbits the phenomenon of local cutaneous reactivity to bacterial filtrates, induce hemorrhage, necrosis and regression of transplantable sarcomas and carcinomas. Ample evidence has been accumulated (Gratia and Linz, Shwartzman and Michailovsky, and Aptiz) to show that the factors responsible for this phenomenon in tumors are identical with those necessary for the phenomenon in rabbits. On the other hand, peptone, histamine, gold chloride with sodium chloride ($AuCl_4\ Na+2H_2O$) and the venom of Crotalus adamanteus (Apitz [4]) fail to produce any reaction in tumors in spite of the considerable damage elicited by the two later preparations in the capillaries of normal tissues and organs. In this paper it is shown that the inhibitory influence of infection on the development of sarcoma 180 is conditioned by the ability of the infecting micro-organism to secrete the bacterial factors necessary to produce the phenomenon in rabbits. In this respect, it is also interesting that the infection of the transplant itself with B. enteritidis plays no obvious rôle in the development and growth energy

6. Daels, F.: Arch. f. Hyg. **72**:257, 1910.

7. Comsia, O.: Compt. rend. Soc. de biol. **99**:900, 1928.

8. Karczag, L.; Csaba, M., and Németh, L.: Ztschr. f. Krebsforsch. **33**:371, 1931.

9. Roskin, G., and Exempliarskaia, E.: Ztschr. f. Krebsforsch. **34**:628, 1931.

10. Centanni, E., and Rezzesi, F.: Néoplasmes **5**:211, 1926.

11. Boccolari-Segolini, A.: Ateneo parmense **5**:315, 1933.

12. Lazzarini, L.: Tumori **13**:357, 1927.

13. Castiglioni, G.: Tumori **7**:434, 1933.

14. Torrey, J. C., and Kahn, M. C.: J. Cancer Research **7**:334, 1927.

of the tumor, provided the mice inoculated remain free from the infection. Attempts are under way to determine the effect of infections with certain avirulent micro-organisms on spontaneous tumors in animals and man.

SUMMARY

Spontaneous infection with B. enteritidis and infection induced with rough B. enteritidis of low virulence exert a striking and inhibitory influence on the development of mouse sarcoma 180.

There exists a definite correlation between the ability of a filtrate of a given micro-organism to elicit the phenomenon of local cutaneous reactivity in rabbits and the inhibitory effect of the infecting micro-organism on the development of sarcoma 180 in mice.

A GASTRO-INTESTINAL LESION ASSOCIATED WITH STAPHYLOCOCCIC INFECTION IN MAN

ITS PRODUCTION IN THE RABBIT BY INTRAVENOUS INJECTION OF STAPHYLOCOCCUS TOXIN

R. H. RIGDON, M.D.
AND
W. A. LEFF
DURHAM, N. C.

The abscess is the characteristic lesion produced by staphylococci. Necrotic and hemorrhagic lesions have been observed in the majority of the organs of the dog and the rabbit following intravenous administration of staphylococcus toxin.[1] Mosny and Marcano[2] in 1894 found petechiae in the mucosa of the gastro-intestinal tracts of rabbits which had been given staphylococcus toxin subcutaneously. Borthwick[3] in 1933 observed hemorrhages in the mucosa of the stomachs and duodenums of guinea-pigs and rabbits following oral administration of staphylococcus toxin. Rigdon[1] in 1935 described hemorrhages and necroses in the gastro-intestinal mucosa of dogs and rabbits following the intravenous injection of staphylococcus toxin.

In a review of the literature we have found no record of a case of staphylococcus infection in man in which hemorrhages and necrosis were unassociated with abscesses in the mucosa of the small and the large intestine. Recently we have observed such lesions in two cases of staphylococcic infection in children. In this paper we describe the clinical and pathologic observations in these cases and report the production of a similar hemorrhagic and necrotic lesion in the gastro-intestinal mucosa of the rabbit following intravenous administration of staphylococcus toxin.

CLINICAL AND PATHOLOGIC CHARACTERISTICS OF THE INFECTION IN MAN

CASE 1.—A white girl aged 6 had otorrhea on the left side for five years and during this time two mastoidectomies on the same side. The right ear began to discharge purulent material about two weeks previous to examination. Examina-

From the Department of Pathology, Duke University School of Medicine.

1. Rigdon, R. H.: Arch. Path. **20**:201, 1935.
2. Mosny and Marcano: Compt. rend. Acad. d. sc. **2**:962, 1894.
3. Borthwick, G. R.: Brit. J. Exper. Path. **14**:236, 1933.

tion showed clinical and roentgenologic evidence of bilateral mastoiditis. Bilateral mastoidectomy was subsequently performed. Material cultured from the mastoid cells contained Staphylococcus aureus. The cultures from the blood and spinal fluid were sterile. The white blood cell count on admission was 13,600 with 90 per cent polymorphonuclear neutrophils. Three days before death the white cell count was 5,800 with 90 per cent polymorphonuclear neutrophils. The urine contained a few hyaline and granular casts and an occasional white cell. The stools were examined twice for ova and parasites, but none were found; however, on each occasion there was a strongly positive benzidine reaction. The temperature while the child was in the hospital ranged between 37.5 and 41.7 C. (99.5 and 107 F.). As a terminal event, bronchopneumonia developed, and the patient died seven days after admission.

Autopsy (One Hour and Twenty Minutes After Death).—There was a recent bilateral infected wound of a mastoidectomy with thrombophlebitis of the right lateral sinus and purulent meningitis. Numerous small abscesses were present in both lungs. Bronchopneumonia was evident in the lower right lobe. A slightly blood-tinged fluid was present in the abdominal cavity. Two hundred and fifty cubic centimeters of the fluid was withdrawn. The peritoneum over the lower ileum, cecum and ascending colon was hemorrhagic. Focal areas of necroses and hemorrhages were present in the mucosa, and bloody material filled the lumen of the gastro-intestinal tract. The wall of the ileum in the distal 175 cm. was edematous and hemorrhagic, and the greater part of the mucosa was covered with a diphtheritic-like membrane. Lesions similar to those in the small intestines were present in the cecum and ascending colon (fig. 1 *A*, *B* and *C*.)

In a detailed study of the gastro-intestinal tract the superficial portion of the mucosa was in many places found necrotic and hemorrhagic (fig. 1 *D*). Frequently the red blood cells were not restricted to the mucosa but extended into the submucosa and the muscular portion of the intestinal wall. In some areas of the better preserved portions of the mucosa, the epithelial cells lining the intestinal glands showed pyknosis, and frequently the lumens of the glands were filled with fragmented cells (fig. 1 *E*). In such areas there were no hemorrhages or thrombosed vessels, but in the more diffusely hemorrhagic and necrotic portions of the mucosa some of the capillaries were occluded by a pink-staining material which resembled fibrin and agglutinated red blood cells. Only a few polymorphonuclear leukocytes were present in the mucosa and submucosa. The greatest amount of necrosis and hemorrhage occurred in the lower 175 cm. of the ileum, the cecum and the first portion of the colon. In the former location the lesion was diffuse while in the latter it was focal. Gram-positive cocci and gram-negative bacilli were present in the necrotic areas of the mucosa.

The renal epithelial cells were often pyknotic and fragmented, and the lumens of some of the tubules were filled with albumin, red blood cells and débris. Staphylococci were present in cultures from the cardiac blood, spleen and lungs; cultures from the small intestines showed staphylococci and colon bacilli.

Case 2.[4]—A 13 year old colored boy had pain and swelling of the left ankle, left forearm and left wrist. Six days before examination, while he was standing on a chain it was suddenly jerked, and the left ankle was injured. The following day there was some pain about the ankle, but he continued to walk. Two days after the accident the pain and swelling became so severe that he stayed in bed.

4. This case is included in a paper by one of us (Dr. Rigdon) entitled "Renal Lesions in Staphylococcus Aureus Infections and Their Relation to Acute Glomerular Nephritis," (Arch. Int. Med. **57**:117, 1936).

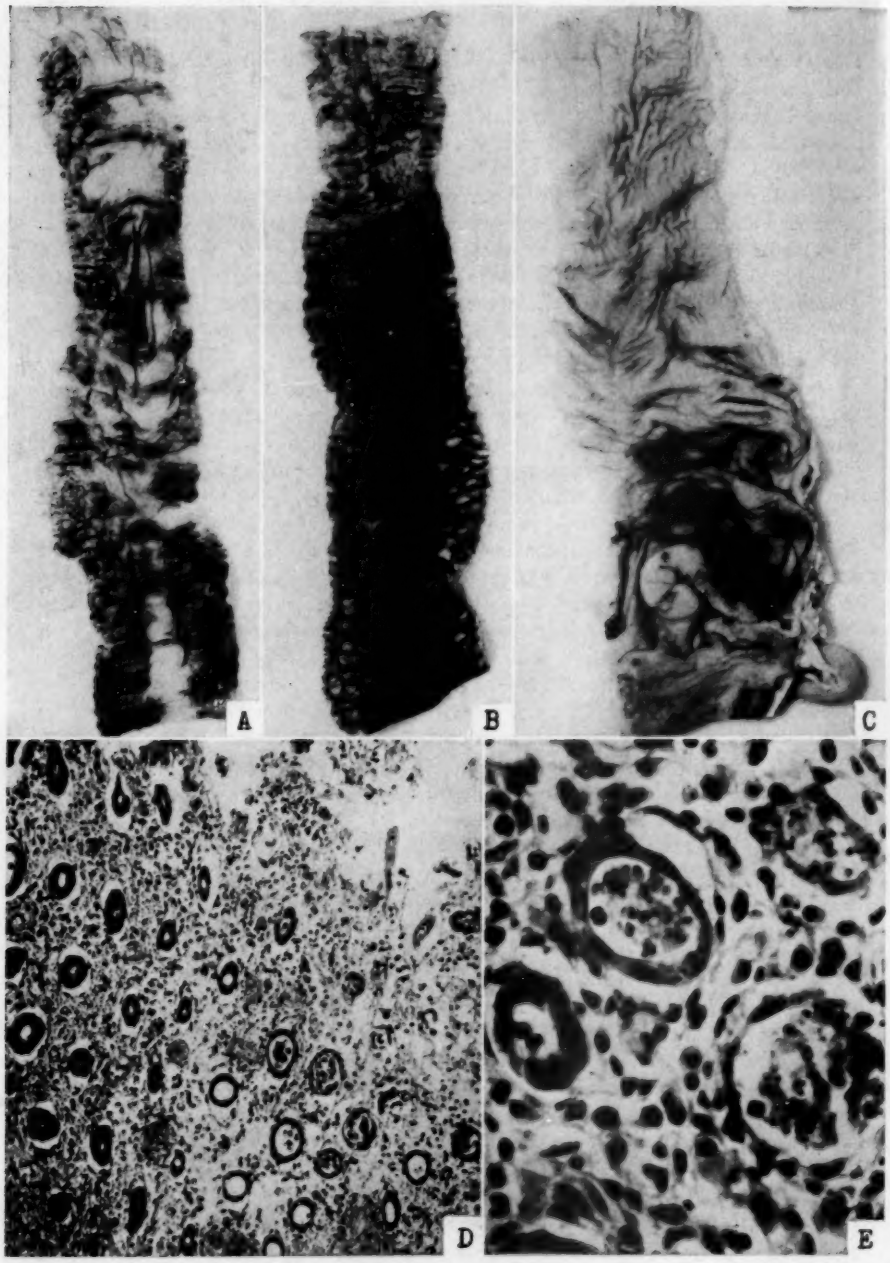

Fig. 1 (case 1: mastoiditis and septicemia due to Staph. aureus).—*A* and *B*, mucosa from the lower ileum. It is necrotic, and the surface is covered by a diphtheritic membrane. *C*, focal areas of necrosis in mucosa from the cecum and ascending colon, similar to that in *A* and *B*. *D*, section of mucosa from the lower ileum showing a focal area of necrosis and hemorrhage. Note the débris in the lumens of the glands and the occluded capillaries. Essentially no leukocytic reaction is present. *E*, pyknosis and karyorrhexis of epithelial cells lining intestinal glands in the ileum. Note the fragmented cells in the lumens of the glands.

During this time the rate of the respirations increased, and pain developed in the chest. The pain and swelling in the forearm and wrist developed approximately sixty hours before death.

The temperature was 40.5 C. (104.9 F.), the pulse rate 160 per minute and the blood pressure 110 systolic and 90 diastolic. There was no abrasion of the skin on the leg. A friction rub was heard on both sides of the chest and also in the precordial region. The left leg was edematous and warm. There was some tenderness about the left wrist. A blood culture was positive for Staph. aureus. The urine was normal. The stools were not examined for blood or parasites. The patient died approximately ten hours after admission to the hospital.

Autopsy (Fourteen Hours After Death).—The left leg was greatly swollen from the knee downward. There was no abrasion or bruise in the skin. The subcutaneous tissues were edematous. In the area of the interosseous septum in the lower half of the leg the tissues were hemorrhagic and necrotic. The periosteum was separated from the shaft of the tibia by a large amount of pus, some of which had infiltrated the adjacent tissues. The marrow in the lower third of the tibia was necrotic.

There was fresh pericarditis; the cultures were positive for Staph. aureus of the hemolytic type. The heart weighed 190 Gm. and showed only a few small hemorrhages in the mitral valve. Both lungs were covered with a fibrinous exudate, and in section they showed many small abscesses. The liver weighed 1,130 Gm. and, when sectioned, disclosed two small abscesses.

The kidneys were swollen, and in the cortex of the left kidney there was an abscess from 5 to 6 mm. in diameter. Many of the tubular epithelial cells were swollen and necrotic, and many contained hyaline droplets. Fat was demonstrated in the tubular epithelial cells with scarlet red. Red blood cells were present in the lumens of many of the tubules. Thrombi were found in few of the afferent arterioles and in the glomerular capillaries.

In the mucosa of the lower ileum and ascending colon were focal areas of hemorrhage and a few leukocytes; a thin diphtheritic-like membrane was present over parts of the mucosa. In the hemorrhagic and necrotic areas the lumens of the capillaries were often occluded with a pink-staining material similar to that in the glomerular vessels and like the substance in the capillaries in the intestinal mucosa in case 1.

PRODUCTION OF GASTRO-INTESTINAL LESIONS IN RABBITS BY INTRAVENOUS ADMINISTRATION OF STAPHYLOCOCCUS TOXIN

A hemolytic strain of Staph. aureus obtained from the pharynx of a patient with the clinical and pathologic lesions of agranulocytic angina was used. The toxin was prepared by the method of Parker, Hopkins and Gunther [5] with a few unessential modifications. The animals used were adult rabbits. No attempt has been made to record the quantity of toxin administered or the frequency of the injections in the individual animal since the potency of the toxin varied in the different preparations.

5. Parker, Julia T.; Hopkins, J. G., and Gunther, A.: Proc. Soc. Exper. Biol. & Med. **23**:344, 1925-1926.

Gastro-intestinal lesions were observed in twenty-five rabbits in a series of one hundred receiving the toxin intravenously. There was a considerable variation in the susceptibility of the rabbits to the toxin, and only a part of those that succumbed had intestinal lesions. Certain rabbits underwent a transitory illness from which they completely recovered, while others died without visible intestinal lesions. There was no relationship between the amount of toxin injected and the occurrence of intestinal lesions or the frequency with which death occurred following the administration of the toxin; 0.5 cc. was a lethal dose for some rabbits while others survived 1 cc. The weight of the animals was approximately the same. The symptoms varied. Sometimes there was generalized weakness with loss of appetite and bloody diarrhea. A few of the animals had convulsions before death. Frequently after large quantities of toxin were given the rabbits had convulsions and died within five minutes.

The lesions in the gastro-intestinal tract were always located in the first portion of the colon and infrequently in the stomach and small intestine. The line of demarcation between the necrotic and the normal mucosa at the junction of the first and second portions of the colon was an impressive feature of the process (fig. 2 *A*).

There is an anatomic difference in the first two segments of the colon.[6] In the first segment there are three Taeniae coli and many sacculations, the wall is thicker than in any of the remaining portions of the colon, cecum or small intestines, and there are more blood vessels per unit of surface area and a richer capillary bed (fig. 3 *E* and *F*).

The degree of damage to the mucosa of the intestinal tract varied in the different rabbits. Usually the necrosis occurred in the distal portion of the first segment of the colon and was either focal or diffuse. In one rabbit an area of necrosis similar to that in the colon was located in the cardiac portion of the stomach.

Following the injury to the endothelial cells of the capillaries the cells lining the intestinal glands apparently were next to show the effect of the toxin. As a result of this injury there were all types of bizarre nuclei and many fragmented cells (fig. 2 *C*). The disintegrated epithelial cells found their way into the lumens of the glands and on to the mucosa, where they formed a diphtheritic-like membrane. Coagulative necrosis of the epithelial cells lining the glands was a frequent observation in rabbits that lived for several hours after receiving the toxin.

In addition to the necrosis we frequently observed congestion, edema and hemorrhage in the mucosa of the first portion of the colon. Some

6. Bensley, B. A.: Practical Anatomy of the Rabbit, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1926.

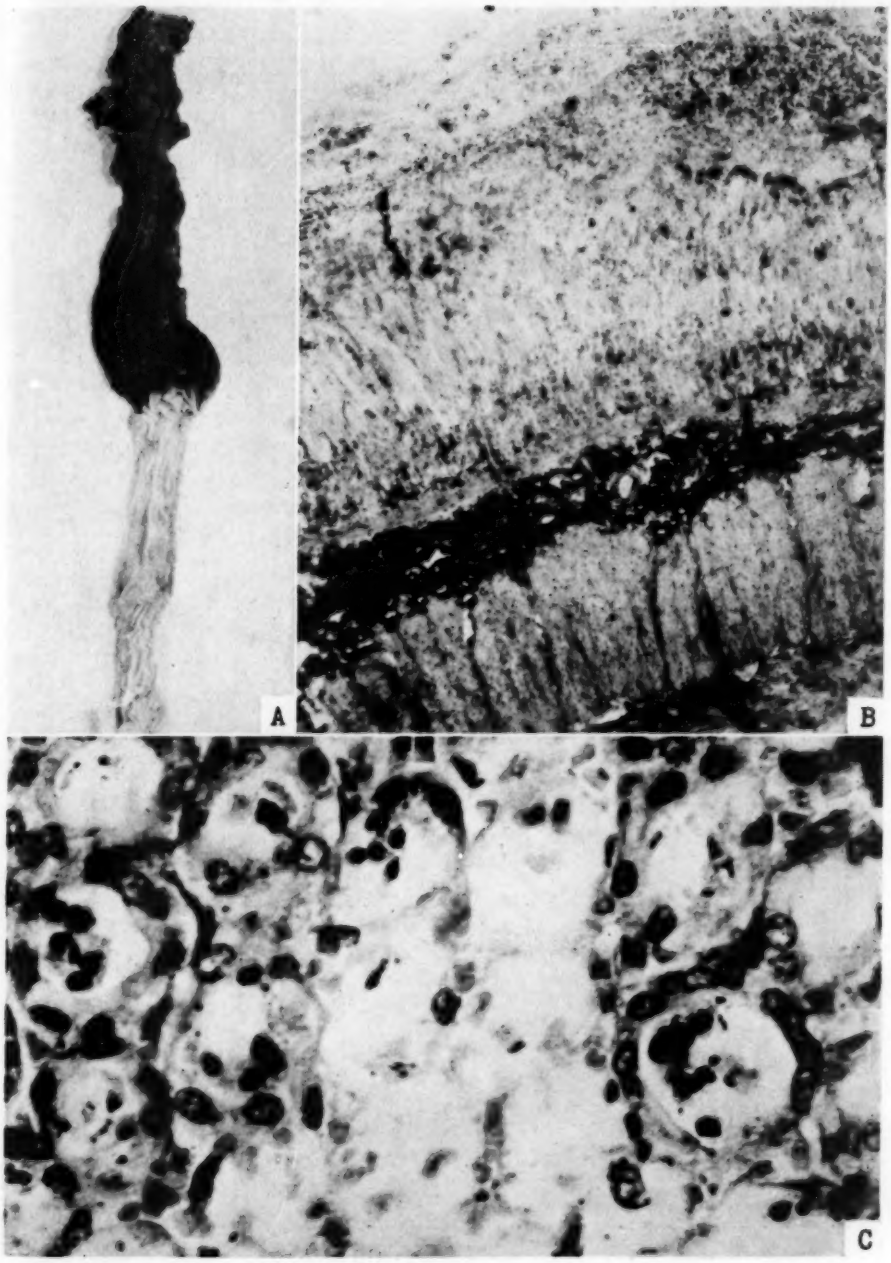

Fig. 2.—*A*, the colon from a rabbit that received one intravenous injection of staphylococcus toxin and died sixteen hours later. Note the anatomic difference and the line of demarcation between the necrotic and hemorrhagic mucosa in the first and the normal mucosa in the second segment of the colon. *B*, coagulative necrosis of the mucosa and a diphtheritic-like membrane on the surface of the colon in a rabbit that received two intravenous injections of staphylococcus toxin during a period of twenty-four hours and died fifty hours after the first injection. Considerable hemorrhage is present in the submucosa. *C*, pyknosis, karyorrhexis and necrosis of the epithelial cells lining glands in the colon of a rabbit that received staphylococcus toxin intravenously.

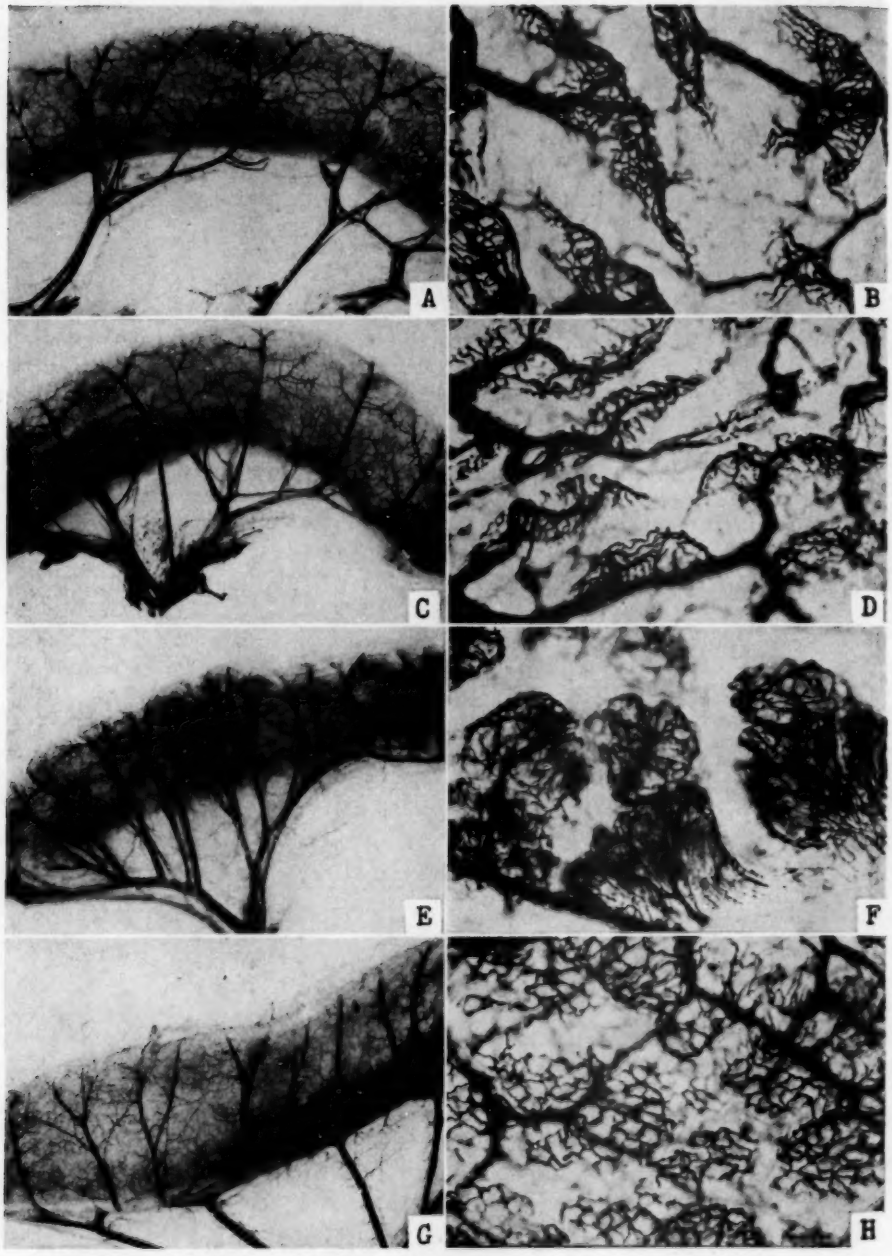

Fig. 3.—India ink injection preparations illustrating the vascular supply of the rabbit's intestine: *A* and *B*, jejunum; *C* and *D*, ileum; *E* and *F*, first segment of the colon; *G* and *H*, second segment of the colon. The larger number of blood vessels and the more diffuse capillary bed are found in the mucosa of the first portion of the colon. All segments are photographed at the same magnification.

of the blood vessels in the mucosa and submucosa were distended with red blood cells. The greatest numbers of thrombosed capillaries were found in the necrotic portions of the colon; the thrombi appeared to be formed by agglutinated red blood cells and fibrin. Fragmented epithelial cells, fibrin, red blood cells and leukocytes were mixed with some of the intestinal contents and lay on the mucosal surface of the intestine. Gram-positive and gram-negative cocci and bacilli were present in the superficial portions of the necrotic mucosa and the diphtheritic-like membrane. Ova of trematodes were present in the mucosa of the colon in some of the rabbits.

Petechiae were the only lesions found in the small intestines of the rabbits given the injections of toxin. These hemorrhages were more diffuse in the mucosa of the ileum. No pathologic change was present in either the cecum or the second and third segment of the colon.

In each of ten rabbits the colon was ligated and severed at a point from 2 to 3 cm. distal to the cecum. Immediately following the operation a small amount of staphylococcus toxin was injected intravenously, and the animal was put to death seventy-two hours later. Hemorrhages and necroses were present in the mucosae of the colons similar to the lesions in other rabbits receiving the toxin. No pathologic lesion was present in the intestinal tract of any control animal.

An attempt was made to study the distribution of the blood vessels in the small and large intestines by the injection of india ink (fig. 3). Two normal rabbits and two which had been given toxin were used for this study. Immediately after death the descending aorta was ligated and a trocar placed in the vessel. Then warm saline solution was injected into the vascular system until the fluid returned clear and pink. India ink was then injected into the aorta until the organs were grayish black. The entire animal was submerged in 8 per cent formaldehyde solution for twenty-four hours, and then small portions of the intestines were removed and dehydrated by soaking in a series of alcohol-water mixtures increasing in alcohol concentration from 50 to 100 per cent, and placed in benzene and methyl salicylate. The india ink preparations in animals that had received the toxin were unsatisfactory because of our inability to remove the red blood cells from the tissue.

COMMENT

At no point in the intestinal mucosa of the two children was there anything to suggest that the hemorrhages, necroses and thrombi were a result of the action of bacteria per se. It seems that these lesions can be adequately explained by the action of staphylococcus toxin on the endothelial cells of the capillaries and on the other cells in the mucosa. The primary focus of infection in each case coupled with the accompanying septicemia, when present, provided an adequate source of toxin.

In both children the illness ran a septic course while they were in the hospital, and obviously they were very ill. In case 1 the stools on two occasions contained a large amount of blood but no ova or parasites. In case 2 the stools were not examined for blood. Neither the first nor the second patient while under observation gave any clinical manifestations of enterocolitis.

The lesions in the intestinal mucosa of the rabbits following intravenous administration of staphylococcus toxin were focal, degenerative and hemorrhagic. From a histologic study of the lesions it appears that the toxin exerts its effect on the endothelial cells lining the capillaries and also on the individual cells in the mucosa.

The focal character of the lesions may be explained as due to an injurious agent circulating in the blood and damaging the endothelial cells lining the capillaries. The most extensive damage occurs in capillaries in which the circulation is diminished or temporarily at a standstill at the time the irritant reaches them, and therefore the toxin acts on them with greater intensity; so much damage is done to the walls of the capillaries that a free transudation of the toxin takes place into the tissues, resulting in focal necroses. Following the injury to the walls of the capillaries there is an extravasation of blood into the tissues. The thrombi in the capillaries form after the injury to the endothelium and are found usually in areas of extensive necrosis and hemorrhage.

It is of interest to note that following intravenous injection of staphylococcus toxin a lesion is always present in the first portion of the colon and rarely in the mucosa of the stomach or of the small intestine. If the necrosis of the intestinal mucosa is a result of the action of the toxin on the cells, and the poisonous agent is brought to the capillaries by the blood, then the greatest amount of injury should occur in the segment with the largest blood supply. According to our studies on the rabbit, the first portion of the colon has the greatest number of blood vessels per unit of surface area and also possesses the richer capillary bed. A larger supply of blood to the first segment of the colon is consistent with the physiologic function of the colon. Starling [7] stated that in some herbivorous animals a very large part of the process of digestion and absorption occurs in the colon and cecum. Apparently the histologic structure of the first portion of the colon is superior, from the point of view of absorption, to that of the remaining portion of the colon, the small and the large intestine.

The lesions in the colons of some of the rabbits suggest that the damage may be produced by staphylococcus toxin excreted into the

7. Starling, E. H.: Principles of Human Physiology, ed. 5, London, J. & A. Churchill, Ltd., 1930.

small intestine and cecum. Such a mode of development of the lesions appears to be unlikely however, since similar hemorrhagic and necrotic changes were present in rabbits in which the proximal end of the colon was ligated and severed previous to the administration of the toxin.

The occurrence of necrosis and hemorrhage on the basis of capillary obstruction appears unlikely since fragmentation of epithelial cells and hemorrhages occur in areas of the mucosa in which there is no evidence of an occluded vessel.

The lesions produced in the rabbit by intravenous injection of staphylococcus toxin are not limited to the mucosa of the stomach and intestines but are present in the kidney, liver, lungs, heart and brain.[1] Recently Rigdon [4] described thrombi in the capillary loops of the kidney, glomerular adhesions, degeneration of renal epithelial cells and blood in the lumens of the renal tubules in cases of staphylococcus infection in man. These lesions were interpreted as a result of the action of staphylococcus toxin.

All the lesions in the rabbit following intravenous administration of staphylococcus toxin suggest that this toxin exerts its effect primarily on the endothelial cells lining blood vessels, especially on those lining the capillaries, and secondarily on the surrounding tissue. All the cells do not react alike to the poisons, not even all the epithelial cells in the same organ.

The lesions in the intestinal tract of the rabbit following intravenous administration of staphylococcus toxin are identical with those in the two patients who had staphylococcus infection. From these observations it appears very likely that staphylococcus toxin was the etiologic agent in producing the intestinal lesion in the cases reported.

SUMMARY

In some infections by Staph. aureus in man a toxin is produced by the organism which enters the general circulation and injures the capillary endothelium and the cellular constituents of the intestinal mucosa.

Following intravenous administration of staphylococcus toxin to the rabbit a lesion is produced in the colon similar to the intestinal lesion found in certain cases of staphylococcus infection in man.

It appears that the injury to the intestinal mucosa is a result of the direct action of the toxin on the endothelial and epithelial cells. The first evidence of damage is a swelling and necrosis of the endothelial cells lining the capillaries. This is followed by pyknosis and karyorrhexis of the epithelial cells lining the intestinal glands.

The localization of the lesion in the first portion of the colon of the rabbit seems adequately accounted for on the basis of the greater vascularity of this segment of intestine.

ADENOSQUAMOUS CELL CARCINOMA OF THE INTESTINE (COMBINED ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA)

REPORT OF A CASE WITH A REVIEW OF THE LITERATURE

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Heterologous neoplasms have been subjects of investigation in pathologic anatomy for over half a century. Such tumors are not uncommon in some locations, for example, the kidney, but in other organs they are extremely rare. The adenosquamous cell carcinoma of the ascending colon reported here belongs to the rare group. The comment, which follows a review of cases previously published, summarizes what has been contributed to the understanding of the pathogenesis of such conditions.

REPORT OF A CASE

M. K., 49 years old, a housewife, was admitted to the New York Post-Graduate Medical School and Hospital, April 24, 1935. In 1920 she underwent a cholecystomy for gallstones. Of five pregnancies, one was terminated by an induced abortion. Beginning in May 1934, the patient noted progressive generalized weakness. Her weight fell from 210 to 165 pounds (95.3 to 74.9 Kg.) (November, 1934), and attacks of dizziness occurred intermittently. The appetite, previously good, was poor for a fortnight, and she had been troubled by "gas in the lower bowel" for two months. Her habitual constipation, relieved by mineral oil, remained unchanged. There was no history of vomiting, blood or tarry stools.

Examination on admission revealed pallor, and the general appearance suggested chronic disease. A mass, about 18 by 10 cm., was palpated in the right lower abdominal quadrant. It was hard, nodulated, elongated, not tender and apparently not attached to the uterus or the right adnexa. The clinical impression was that of carcinoma of the cecum or colon. A roentgenologic gastro-intestinal examination led to a diagnosis of "tumor in the right side of the abdomen involving the colon at the hepatic flexure." The patient was given a transfusion of 500 cc. of blood May 1, 1935, four hours before a laparotomy.

The abdomen contained a large quantity of ascitic fluid. A large mass was seen springing from the posterior aspect of the ascending colon, which extended into the mensentery and on to the adjacent first portion of the jejunum and mid-ileum. The terminal 15 cm. of the ileum, the cecum and the proximal half of the transverse colon were resected. A lateral anastomosis was then performed between the ileum and the transverse colon.

The postoperative condition was poor and did not improve after a colostomy. The general condition became worse, the temperature rose, reaching 107.8 F., and she died on May 6, 1935, five days after operation.

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At necropsy, two hours after death, there was no evidence of neoplasm. The metastases on the small intestine, described at operation, had apparently been thoroughly removed at that time. About 6 cm. proximal to the anastomosis of the ileum and the transverse colon there was marked kinking of the intestine. A marked dilatation of the small intestine began at this point. Although the anastomosis was water tight, the serosal surface was covered with a faintly greenish-yellow purulent exudate. A diffuse peritonitis of similar character was present, in the fluid of which nonhemolytic streptococci predominated. There were also hemolytic and nonhemolytic Bacillus coli-acidi-lactici. The latter were present in a specimen of blood removed from the right auricle of the heart.

Over the diaphragmatic pleura and the base of the right lower pulmonary lobe there was a tenacious exudate similar to that on the peritoneum. There was healed mitral endocarditis without functional disturbance. The spleen showed acute swelling from infection, and the heart, liver and kidneys, cloudy swelling. The lumen of the gallbladder was filled by eight faceted combination stones. On the right side there were two renal pelves and two ureters, each ureter with a separate opening into the bladder.

DESCRIPTION OF SPECIMEN

The specimen removed at operation included 14 cm. of terminal ileum and the appendix, which showed no abnormality. The cecum as well as the colon beyond the neoplasm was dilated and the wall thinned, but the intestinal plicae were still prominent. Beginning about 5 cm. from the ileocecal valve was a neoplastic mass which involved the colon for a distance of from 5 to 8 cm., completely encircling and markedly narrowing its lumen, the diameter of which was 1.5 cm. proximally and 1 cm. distally. On its inner surface the neoplasm was ragged and irregular. In the proximal third the surface was gray, coarsely villous, ulcerated and hemorrhagic, while distally it was coarsely lobulated, overhanging the surrounding mucosa at its periphery.

On section, all coats of the intestine were invaded by the tumor, which, for the greatest part, was formed of pearly gray gelatinous tissue in a loose connective tissue meshwork. There were, however, areas of different character in the distal portion (fig. 1). These were superficial and were dense, homogeneous, moderately firm and grayish yellow, suggesting thickened epidermis, the largest 1.5 cm. thick.

On the posteromedial surface, externally, the gelatinous tumor had broken through. It was from this area that the loops of small intestine had been freed at operation. Just lateral and distal to this point, there were several lymph nodes, the largest 1.5 cm. in diameter. The hepatic flexure of the colon was markedly angulated because of the retraction of the great omentum, which was included laterally in the adhesions about the neoplasm.

Sections taken from different areas in the neoplasm for microscopic study showed a varied picture. Apart from edema and infiltration of the stroma by lymphocytes and plasma cells, the intestinal wall proximally showed no marked alterations. The normal mucosa (fig. 2 *a*) was abruptly replaced by the neoplasm, which in this area had the character of adenocarcinoma. The columnar cells, which formed strands and tubular structures, were hyperchromatic, with deep-staining vesicular nuclei. Mitoses were numerous. More deeply situated, irregularly circumscribed by narrow bands of dense, moderately cellular connective tissue, were cystlike areas in which the cells were distended with a loose, faintly basophilic material and the cytoplasm correspondingly reduced. As a result, nuclei with small rims of cytoplasm appeared free in the colloid material (fig. 2 *b*). In general, the stroma of the neoplasm, dense and cellular, was extensively infiltrated by lymphocytes, plasma cells and fewer polymorphonuclear neutrophils,

the cells forming many dense foci. The neoplasm had invaded all coats of the intestine and extended proximally in the submucosa layer, undermining the adjacent healthy mucosa. Within the neoplasm proper, zones of intact normal intestinal glands were still present.

A section taken through the neoplasm in its middle third, where the two light gray areas are seen directly on the lumen in figure 1, showed chiefly colloid areas with numerous signet ring cells, but the light gray areas were of an entirely different character (fig. 2*c*). In these there were interlacing columns and islands of polyhedral cells, and none of the columnar type. The peripheral cells of the larger

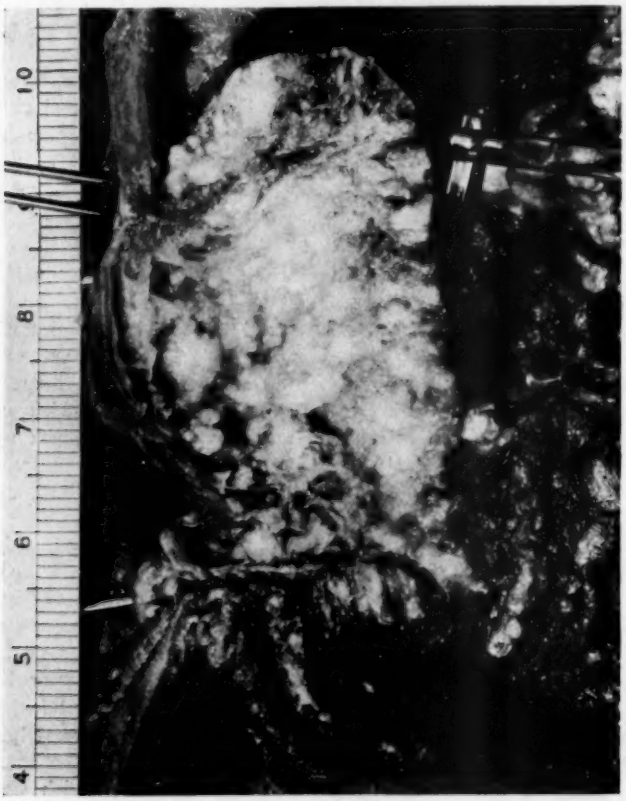

Fig. 1.—Sagittal section of neoplasm (colloid carcinoma) and adjacent uninvolved colon showing areas of squamous epithelium; × 1.5.

formations, similar to those forming the smaller columns (fig. 3*a*), were small with indefinite cell boundaries. The cytoplasm, faintly basophilic to eosinophilic, had a fine basophilic network. The nuclei, which had a diameter from three to four times that of an erythrocyte, were deep-staining, vesicular, with one large and not infrequently several smaller nucleoli, and the chromatin meshwork together with smaller chromatin granules was prominent.

The centrally placed cells, which composed the major portion of the columns and islands, were much larger than the peripheral cells, many four times the size of the latter. The cytoplasm, delicately reticulated and faintly eosinophilic, was denser in a zone directly about the nucleus and at the cell periphery. The nucleus, about twice that of the peripheral cell, was even more vesicular, with an eccen-

trically placed large nucleolus and fine chromatin granules directly on the distinct nuclear membrane. Moderate numbers of mitotic figures were present in both central and peripheral cells. In isolated small areas, there was cell disintegration with nuclei free in spaces bounded by the surrounding unaltered cells. Concentric lamellations, epithelial pearls, were few and in isolated areas.

In the squamous cell portion of the neoplasm, just described, intercellular bridges were distinctly recognized. In one area the polyhedral cells merged with greatly flattened cells with interposed transition forms. The flattened cells, with

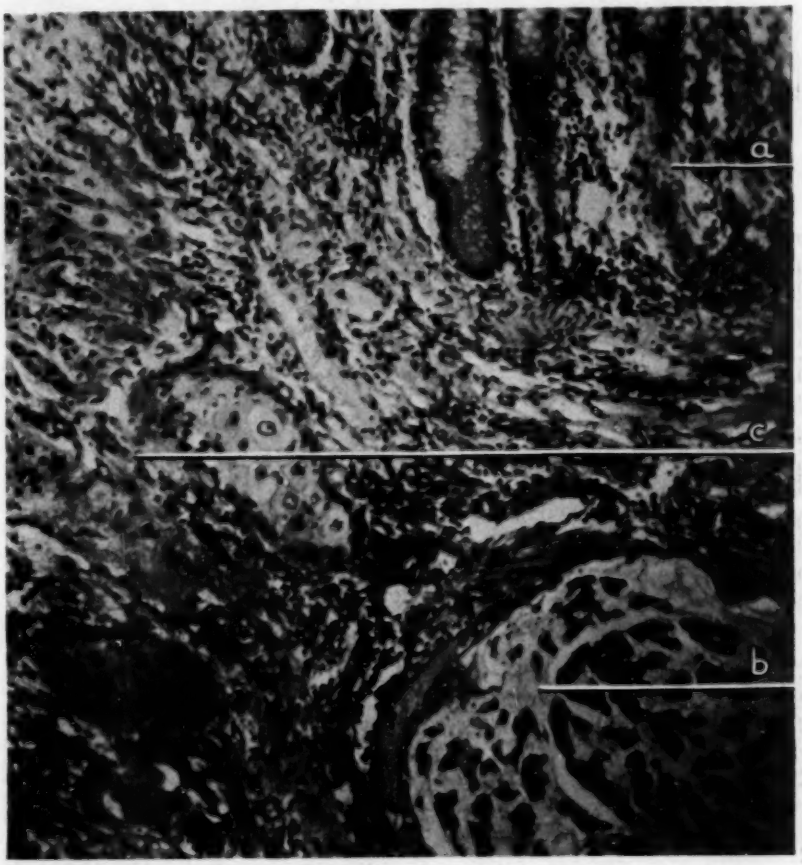

Fig. 2.—Junction of normal columnar epithelium of colon (*a*) with both types of neoplasm, colloid carcinoma (*b*) and squamous cell carcinoma (*c*); × 100.

indefinite or unrecognizable boundaries, had deeply eosinophilic, dense, refractile cytoplasm. Their small round nuclei were indefinitely vacuolated, and no nucleoli were present. About the nuclei there were irregular-sized, deeply basophilic to neutrophilic granules, strongly suggestive of keratohyalin. With the Van Gieson stain the polyhedral cells were faintly yellowish gray, the flat cells orange yellow to brownish yellow, the non-nucleated cell a deeper brown, and the granules a deep orange-brown, all indicative of keratin derivatives.

On the surface the neoplasm was ulcerated and necrotic. Here there was little stroma present, so densely packed together were the epithelial masses. More

deeply the stroma was scanty and formed of loose, highly cellular connective tissue. At its base, the squamous cell area was indefinitely separated from the colloid area by a zone from two to three cells thick. The cells, polyhedral, were extremely pale, and at their periphery they were not to be distinguished from those with colloid. More deeply, about 10 mm. from the area just described, there were other fields of squamous cell carcinoma. These were in part separated from the areas of colloid carcinoma by dense hyalinized connective tissue bands. In one

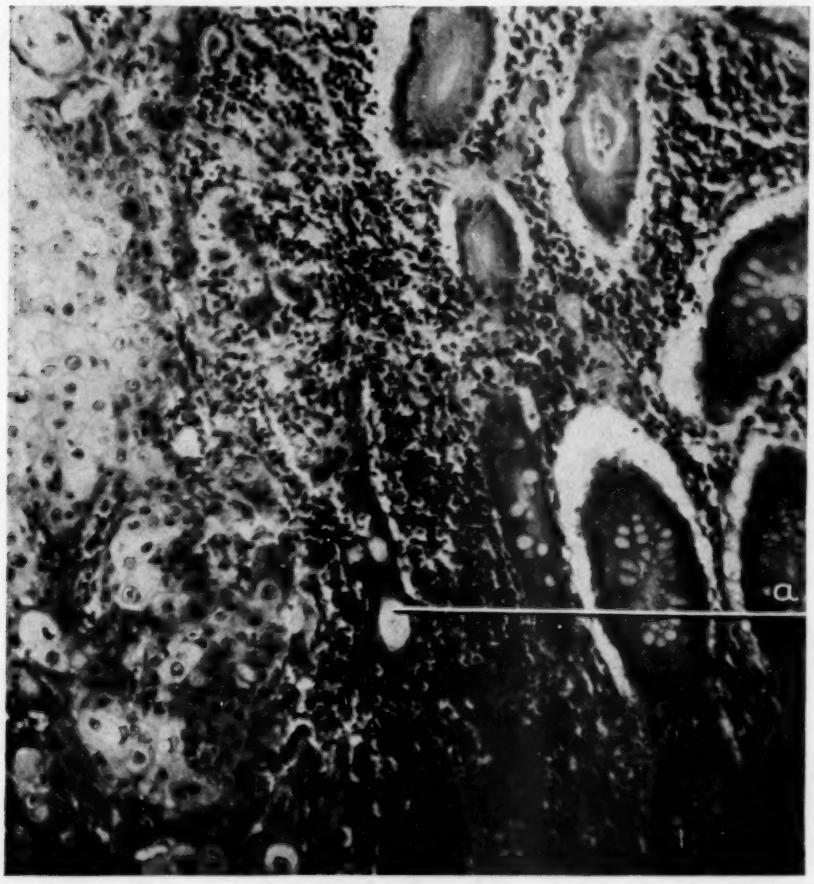

Fig. 3.—Junction of normal colon mucosa and squamous cell carcinoma, showing transition (?) forms (*a*); × 100.

area, however, the partly necrotic squamous cells desquamated directly into the colloid and were identifiable in that medium.

At the junction of the squamous cell carcinoma with the distal unaltered intestine were a few glands formed of cells varying in shape from cuboidal to polyhedral with deeply eosinophilic cytoplasm (fig. 3). One or two columnar cells were also present. The lumens contained eosinophilic amorphous débris. These were the only evidences of a possible transition of cylindric to squamous epithelium.

The regional lymph nodes showed only hyperplastic alterations. No metastases were found.

REVIEW OF THE LITERATURE

Apart from the esophagus, gastric cardia and rectum, squamous cell neoplasms or neoplasms of the gastro-intestinal tract containing squamous cell elements have been infrequently recorded or reviewed.[1] Borst [2] has an illustration of a cornifying gastric carcinoma, which is referred to in the text but without data. Calderara's [3] first case was one of squamous cell carcinoma at the pylorus. There were massed strands of cells, peripherally multilayered, cylindric, with small oval nuclei. An intermediate zone was formed of polymorphic cells. Centrally the cells were flatter, with homogeneous cytoplasm, and formed true epithelial pearls. Calderara believed that only after the formation of the neoplasm did alteration to squamous epithelium take place.

Herxheimer's [4] paper was the most comprehensive for many years. In it he reported adenosquamous cell carcinoma of the uterus, pancreas, stomach and cecum which he termed *Adenokankroid,* a designation rarely used at the present time. The same may be said of the term "adeno-acanthoma." In his second case a stenosing neoplasm was found at the pylorus with miliary nodules on the serosa and two swollen glands behind the pylorus. It extended on to the duodenum but was not adherent to the pancreas. At necropsy no carcinoma was found elsewhere. The major portion of the neoplasm proved microscopically to be the "usual gastric adenocarcinoma." Some of the glandular elements were formed of irregularly tall cells with equally irregular nuclei and large, clear, vacuolated cytoplasm. The cells of some of the gland elements were directly continuous with flatter cells which were without distinct borders and had dark irregular nuclei, centrally placed. The lumens of the glands were small or absent. Deep in the tumor, as well as at its periphery, there were solid cell nests with flattened cells centrally, where no nuclei were present, but where keratin and intercellular bridges were present, as well as fine fibrillation in the cells (*Epithelfasern*). All types of transitions were seen in some glands, distinctly showing adenomatous and squamous cell elements as portions of the same tumor.

Kaufmann [5] briefly reported a primary cornifying squamous cell carcinoma in a 42 year old man. The "carcinomatous ulcer" on the posterior gastric wall infiltrated the liver and gradually dwindled as it approached the cardia.

The three cases of Klebs [6] probably do not belong in this category since the areas of squamous cell carcinoma in the stomach were interpreted as implants from malignant neoplasms of the same type in the esophagus, cheek and base of the tongue.

Lubarsch [7] described an adenocarcinoma of the pylorus with adenocarcinoma and squamous cell carcinoma metastases in distant lymph nodes. Further study

1. Oberndorfer, S.: Heterologe Karzinome des Darmes, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, pt. 3, p. 897.

2. Borst, M.: Die Lehre von den Geschwülsten, Wiesbaden, J. F. Bergmann, 1902, vol. 2, pp. 645 and 665.

3. Calderara, A.: Virchows Arch. f. path. Anat. **200**:181, 1910.

4. Herxheimer, G.: Beitr. z. path. Anat. u. z. allg. Path. **41**:348, 1907.

5. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 9 and 10, Berlin, W. de Gruyter & Co., 1931, vol. 1, p. 657.

6. Klebs, E.: Handbuch der pathologischen Anatomie, Berlin, A. Hirschwald, 1869, vol. 1, p. 190.

7. Lubarsch, O.: Verhandl. d. deutsch. path. Gesellsch. **10**:198, 1906.

of the primary site demonstrated a single area of squamous cell carcinoma with intercellular bridges and epithelial fibrillation.

A case of pyloric adenosquamous cell carcinoma in a 67 year old woman was reported by Oberling and Wolf.[8] All the abdominal viscera were involved in a single mass which was partly viscid. The necropsy disclosed gelatinous masses at the pylorus which were continuous with a homogeneous white neoplasm invading all layers of the gastric wall. On section the lumen surface of the tumor was fungating and ulcerating. The liver had numerous viscid metastases as did the peritoneum. One nodule was seen in the spleen. Microscopically the pyloric mass was a "polymorphic carcinoma," chiefly cylindric cell adenocarcinoma. There were isolated islands of squamous cell carcinoma with no transitions seen between the columnar and the squamous cells.

Pasternack [9] recently published a report of an "adeno-acanthoma" of the pylorus occurring in a 48 year old seaman with the usual complaints of gastric neoplasm. A laparotomy disclosed a nonadherent pyloric mass, 8 cm. in diameter. At the pylorus there was an ulcerating, vegetating, more or less cornified mass, 9 by 6 by 4 cm., projecting into the lumen of the stomach and tapering off into the hard, leathery adjacent gastric mucosa. Section disclosed whitish-yellow and yellow masses, sharply demarcated from each other, extending through to the serosa but chiefly in the submucosa. The neoplasm was predominantly squamous cell carcinoma showing all degrees of cornification. Other areas showed atypical, hyperchromatic mucosa and glands invading all layers, including vessels and nerves. In two sections, transitions of adenocarcinoma to carcinoma of the squamous cell type were present.

The patient died three and a half months later of intestinal obstruction. At necropsy there was adenocarcinoma with foci of squamous cell carcinoma along the line of the old scar, independent of the columnar cell neoplasm. The latter was present in the omentum, pancreas and two lymph nodes found along the margin of the resected pylorus. No recognizable metastases were present.

Pollack,[10] in a case of gastric adenocarcinoma in a man, found chiefly cylindric and cuboidal epithelium in pulmonary metastases. There were, however, masses of squamous epithelium with intercellular bridges, concentric lamellation and beginning cornification. Reviewing Pollack's case, Herxheimer was of the opinion that a more careful examination of the primary neoplasm would probably have revealed areas of squamous cell carcinoma, since neither in Lubarsch's case nor in his own were such areas present in all parts of the tumor.

In Plenge's [11] first case, that of adenosquamous cell carcinoma of the duodenum in a man of 58 years, there was infiltration of the head of the pancreas and resultant compression of the bile and pancreatic ducts by a saucer-sized, centrally necrotic carcinoma of the duodenum about the papilla of Vater. The neoplasm was formed of strands and plaques of polyhedral squamous cells with epithelial fibrillation, intercellular bridges and, in some areas, epithelial pearls. In a few places, especially close to normal intestine, there were glandular formations with some lumens lined in part by cylindric cells with transitions to flattened cells. There were metastases to the nodes of the liver and to its hilus and about the pancreas, as well as to both adrenals.

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8. Oberling, C., and Wolf, M.: Bull. Assoc. franç. p. l'étude du cancer **16**:68, 1927.

9. Pasternack, J. G.: Am. J. Path. **11**:541, 1935.

10. Pollack, K.: Beiträge zur Metaplasiefrage, in Arbeiten aus der pathologisch-anatomischen Abteilung des königl. hygienischen Instituts zu Posen, Wiesbaden, J. F. Bergmann, 1901, p. 154.

11. Plenge, C.: Virchows Arch. f. path. Anat. **264**:370, 1927.

Herxheimer [4] and Plenge [11] each reported a case of adenosquamous cell carcinoma of the pancreas. In Plenge's case no transition between columnar and squamous epithelium was seen nor were the two types of tumor seen together in the same metastasis.

There is no history recorded of Herxheimer's [4] third case, one of "carcinoma cylindrocellulare cancroidale" of the cecum. Throughout the neoplasm, which was predominantly adenocarcinoma, colloid type, there were round to oval areas formed of lamellated, poorly staining flat cells with keratin and intercellular bridges. No definite transition zones were seen.

Humiston and Piette's [12] case is the only one of its kind reported in the intestinal tract—a case of "cholesteatoma" of the cecum. A man, 31 years old, presented a clinical picture of recurrent appendicitis. A tender mass was palpated in the right lower abdominal quadrant. At operation the inflamed appendix was adherent distally to the tumor, which was encysted in the cecal outer wall and did not communicate with the intestinal lumen. The neoplasm, 5 cm. in diameter, was a loose silvery-white sphere with cornifying squamous cells and cholesterol crystals as content. The inner layer of the wall was formed by two or three strata of flat squamous epithelium, well preserved only in a few places, and in one area it dipped down into the underlying tissues in columns composed of from twenty to thirty layers of "malpighian" cells. The epithelium everywhere was delimited from the underlying connective tissue by a distinct basal membrane. Where epithelium was absent, granulation tissue lined the cavity. In the middle layer there were glands lined by three layers of columnar cells. The outer layer corresponded to the peritoneal connective tissue.

The third case of Plenge,[11] an instance of adenosquamous cell carcinoma of the large intestine, was in a woman of 28 years. In 1924 an inflamed appendix with what was grossly described as a gangrenous tip—no microscopic examination was done—was removed. Shortly after a normal delivery in October 1925 there was pain at the operative site, bloody stools and fever. A fistula soon formed, discharging pus. One month later the area was incised, but the diarrhea persisted. In December 1925 the scar was excised, and at the site of the previous operation thick scar tissue with gray-yellow areas was curetted, which microscopically showed adenosquamous cell carcinoma. The neighboring lymph nodes were hard and enlarged. There was a postoperative fecal fistula, and death, attributed clinically to peritonitis, occurred two weeks later. At necropsy, a necrotic tumor was found at the ileocecal valve, firmly united by necrotic masses to the anterior and lateral abdominal walls. About 7 cm. of cecum was included in the neoplastic mass. The mesentery of the ileocecal valve had a necrotic metastasis, and a smaller metastasis was seen on the peritoneum of Douglas' pouch. The microscopic observations were alike in the necropsy specimen and the curettings. The layers of the intestine were virtually unidentifiable because of extensive necrosis. In the neoplasm there were areas of cylindric cell adenocarcinoma. In many of the glandular structures there was transition to cuboidal cells and to squamous epithelium. In some areas there were solid nests of squamous cells with epithelial fibrillation, intercellular bridges and epithelial pearls. Both cylindric and squamous epithelium were seen in the metastases.

Probst's [13] case, one of adenosquamous cell carcinoma of the sigmoid, falls into that borderline group which may perhaps be explained by the presence of ecto-

12. Humiston, C. E., and Piette, E. C.: J. A. M. A. **84**:874, 1925.

13. Probst, O.: Zur Kasuistik heterologer Darmkarzinome. Ein Adenocancroid des Colon sigmoideum, Inaug. Dissert., Würzburg, F. Staudenraus, 1909.

dermal elements in the terminal portion of the intestine. No indication as to the distance of the neoplasm from the anus was given. A man of 60 years had suffered generalized pain and constipation which became progressively worse. Blood was occasionally present. At operation, a retracted circular neoplasm of the sigmoid, freely movable, was found, and two days later the tumor with the adjacent intestine was resected. The neoplasm, about 3 cm. thick, firm, whitish gray, medullary and ulcerated, was composed microscopically of three different cellular structures. The first type was cylindric-cell adenocarcinoma with multilayered papillary projections in some lumens. Another type showed masses of cells varying in shape from round to polyhedral, with a tendency in some areas to the formation of lumens. The cells of the third type, squamous cell carcinoma, had intercellular bridges and zones staining like keratin in which the cells had dense cytoplasm and karyorrhectic nuclei. No epithelial pearls or fibrillation was seen nor were metastases found. There is no mention of transitional forms between adenocarcinoma and squamous cell carcinoma.

Schmidtmann [14] reported several cases of heterotopic carcinoma. Her second case, one of cornifying squamous cell carcinoma of the ileocecal valve, occurred in a 65 year old man. In the right side of the abdomen he had a "crabapple-sized" nonmovable tender mass which grew rapidly. Some of the swollen inguinal nodes had broken down and perforated, discharging a small quantity of pus. There was blood in the stools. The Wassermann reaction was positive. At necropsy a partly ulcerated mass was found in the ascending colon just above the ileocecal valve. The mucosa over the tumor was practically unchanged in most areas. Under the mucosa and invading it were densely packed nests of squamous epithelium with very definite cornification at many points. Neoplastic masses, found only in the inguinal lymph nodes, were, for the most part, necrotic but still identifiable.

COMMENT

Heterotopic neoplasms are, perhaps, more provocative of discussion than homologous new growths, because they are so intimately linked to the problem of the alteration of one type of epithelium to another, whether by metaplasia [15] or prosoplasia. Overgrowth from or inclusion of adjoining epithelium of different type,[16] the inclusion of rests of other embryonal layers and the presence of indifferent cell masses have also been suggested as the factors concerned.[17]

Squamous cell carcinoma of the rectum may be explained by the development of ectodermal rests. Similarly the same neoplastic disease of the uterus may arise from inclusions of cervix epithelium and at

14. Schmidtmann, M.: Virchows Arch. f. path. Anat. **226**:100, 1919.

15. Boyd, W.: Surgical Pathology, ed. 3, Philadelphia, W. B. Saunders Company, 1933, p. 151. Borst.[1]

16. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 717. Karsner, H. T.: Human Pathology, ed. 3, Philadelphia, J. B. Lippincott Company, 1931, p. 667. MacCallum, W. G.: A Text-Book of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932,

17. (*a*) Kawamura, R.: Virchows Arch. f. path. Anat. **203**:421, 1911. (*b*) Loeb, P. W.: Frankfurt. Ztschr. f. Path. **25**:155, 1921. (*c*) Borst.[1] (*d*) Herxheimer.[3] (*e*) Probst.[12]

the gastric cardia from esophageal overgrowth or from rests of stratified squamous epithelium similar to that of the lower part of the esophagus.[18] Such an explanation fails when one is confronted with a neoplasm in the ascending colon, as reported here. Squamous cell tumors of the trachea at the bifurcation may arise from inclusions of esophageal epithelium, since the two structures are so intimately related. At no period of fetal development is the ascending colon related to any structures producing or formed of stratified squamous epithelium.

There have been many adherents of the theory of the presence of indifferent cell masses which, during postembryonal life, differentiate in one or several directions. The case of "cholesteatoma" reported by Humiston and Piette [12] might fall into this category, especially because of the encapsulation of the neoplasm. Herxheimer,[4] who attempted to explain all heterologous tumors by the theory that they were due to proliferation of indifferent cell masses, believed that the presence of transitional formation supported such a view, despite the fact that prosoplasia and metaplasia could also adequately account for such structures. Fischer-Wassels' pupil, Loeb,[17b] leaning toward Herxheimer's views, wrote that it seemed probable that

> these rare tumors (adenosquamous cell carcinoma) arise directly from indifferent cells, markedly retarded in development (in ontogenetically selected areas), linked with heteroplastic processes. In this connection the epithelial alteration is assumed to be prior to or contemporaneous with the tumor formation. The origin of these tumors from definite, less immature cell forms that in differentiation fairly well approach normally developed cylindric epithelium seems to me to be equally possible. In such a case the epithelial alteration would appear only in the already formed tumor. On the other hand, the origin of the tumors from cell stages produced by different degrees of differentiation of definitely less developed cell forms is indirectly possible, especially in regenerative processes.

Prosoplasia is a "pathologic change of epithelium which consists in a further differentiation beyond the state of local differentiation." [19] Schridde,[20] in an exhaustive study of the epithelium of the esophagus in the human embryo, pointed out "that the entodermal cells of the (fetal) esophagus are capable of producing elements in five different directions with sharply different morphologic characters. These are the pale cylindric cells, then the ciliated cells, further the polyhedral pale

18. Toldt, C.: Sitzungsb. d. k. Akad. d. Wissensch. (Math.-naturw. Cl.) **82**:57, 1880.

19. Schridde, H.: Die ortsfremden Epithelgewebe des Menschen, in Gaupp, E., and Nagel, W.: Sammlung anatomischer und physiologischer Vorträge und Aufsätze, Jena, Gustav Fischer, 1909, no. 6, p. 11; in discussion on Lubarsch.[6]

20. Schridde, H.: Die Entwicklungsgeschichte des menschlichen Speiseröhrenepitheles und ihre Bedeutung für die Metaplasielehre, Wiesbaden, J. F. Bergmann, 1907.

cells, then *Faserzellen* (cells with cytoplasmic fibrillation) and finally the cylindric mucous cells."

With that as a basis, he classified the various types of epithelium at different levels of differentiation, each potentially alike and capable of differentiating to another and higher level. For example, he explained the frequent presence of cornified areas in the esophagus by placing noncornified stratified squamous epithelium at a slightly lower level of differentiation than the cornifying type. To Schridde, the wide zone of differentiation separating stratified squamous epithelium, on the higher level, from transitional epithelium, on the lower level, was an adequate explanation for the rarity of leukoplakia on surfaces covered by the latter type of epithelium. All epithelial surfaces were alike, according to Schridde, because all were formed of cells with cytoplasmic fibrillation (*Epithelfasern*) and with tonofibrils. The presence of tonofibrils in epidermis cells, so well demonstrated by him,[19] is accepted, but apparently no one has confirmed his observation of fibrillation in other epithelial cells. As Lubarsch [21] pointed out, because of that lack of confirmation prosoplasia as an explanation of alterations of epithelium in postembryonic life collapses.

Metaplasia has been suggested as a more satisfactory explanation of the process of formation of heterologous epithelial neoplasms. It is the "alteration or substitution of specific cellular . . . structures by differently formed, equally definitely differentiated structures of similar type cells." [21] True metaplasia is to be sharply differentiated from other forms of alloplasia, particularly pseudometaplasia, in which cells change their form. This may take place in columnar epithelium in the course of accommodation, in which cells become narrower, flatter, and look like those of true stratified squamous epithelium. The metaplastic process is not a direct one. The offspring of the original cells are less differentiated than their ancestors (neoplastic phase), but their offspring in turn proceed to differentiate in the direction of the new epithelium (metaplastic phase).[2] The new epithelium, as has been indicated in studies of leukoplakia of the urinary tract, may be maldeveloped or incomplete in elements.[22] This fact, as well as the neoplastic phase of metaplasia, accounts for the presence of transitional structures in adenosquamous cell carcinoma.

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21. Lubarsch, O.: Die Metaplasiefrage und ihre Bedeutung für die Geschwulstelehre, Arbieten aus der pathologisch-anatomischen Abteilung des königl. hygienischen Instituts zu Posen, Wiesbaden, J. F. Bergmann, 1901, p. 205.

22. Malherbe, A., and Pasquereau, X.: Leucoplasie de la vessie, in Pousson, A., and Desnos, E.: Encyclopédie française d'urologie, Paris, Gaston Doin & Cie, 1921, vol. 4, p. 539. Putschar, W.: Leukoplakie der Harnwege, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1934, vol. 6, pt. 2, p. 479.

Metaplasia takes place under a variety of conditions. Fütterer [23] removed the mucosa and muscularis mucosae from the stomachs of rabbits. After a time, the defects in some of the animals were covered by stratified squamous epithelium. There is no statement of how close the areas of operation were to the esophagus. Metaplasia finds its most favorable soil in the marked growth energy and alterations of the regenerative process in long-standing inflammations, mechanical irritations [17a] and neoplastic diseases, when a rigorous specificity of cells cannot be maintained at all times.[24] The metaplastic process need not stop in all or in any part of the involved area at a simple alteration of epithelium but may continue to produce a malignant neoplasm, even of a mixed type, as in the case reported in this paper. As Schmidtmann [14] pointed out, apart from the esophagus and the rectum, heterologous carcinomas of the gastro-intestinal tract are found at sites of stagnation. The pylorus, the adjacent duodenum, the ileocecal valve, the cecum and, in our case, the ascending colon next to the hepatic flexure are such areas. Even Probst's [13] case would fall into this group if the neoplasm were located in the tortuosity of the sigmoid.

The case for metaplasia as contrasted with prosoplasia and its support in fetal conditions has never been better stated than by Wells [25] in his study of squamous cell carcinoma of the renal pelvis.

> When cells assume the proliferative activity that is characteristic of malignancy, they usually lose their more recently acquired functions and retain chiefly the simple vegetative function of proliferation. But when a transitional or columnar epithelial surface becomes squamous through metaplasia, and the same protracted irritation that produced the metaplasia continues until cancer results, we find that the newly acquired property of forming keratin has become fixed and the cancer is a keratinizing, squamous-cell carcinoma. One would expect the epithelium to approach its original, simpler embryonal character, rather than exhibit and retain so profound and recently acquired an alteration as the production of keratin.

SUMMARY

Adenosquamous cell carcinoma of the ascending colon is reported in a woman of 49 years. This type of neoplasm, not common elsewhere in the body, is even rarer in the gastro-intestinal tract. Its occurrence at sites of intestinal stagnation is regarded as the result of metaplasia.

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23. Fütterer, G.: Ergebn. d. allg. Path. u. path. Anat. **9**:706, 1903.
24. Schwalbe, E., in discussion on Lubarsch.[6]
25. Wells, H. G.: Arch. Surg. **5**:356, 1922.

CHRONIC COCCIDIOIDAL MENINGITIS

REVIEW OF THE LITERATURE AND REPORT OF SEVEN CASES

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As a rule coccidioidal granuloma first manifests itself as a focal lesion, the skin or lungs being the primary site of infection. In many cases the infection ultimately becomes generalized, and metastases may be found in various organs or tissues, including the central nervous system and its coverings. In other cases the widespread lesions of a systemic infection are found, although the site first infected is not discoverable. In this group of cases the nervous system is affected in some instances, to the apparent exclusion of all other structures. It is our object in this paper to review the various possible cranial and intracranial lesions provoked by this disease, giving particular attention to that form of chronic meningitis which may develop without clinical evidence of the original focus of infection. It has been our good fortune to study a series of 7 such cases, a brief report of which is made in this paper. In addition, we have summarized the findings in 7 other cases in which the cranial and intracranial lesions were secondary to a known distant focus or systemic infection.

These cases were gleaned from a series of about 15,000 autopsies, over 12,000 of which were performed at the Los Angeles General Hospital and the others by members of the department of pathology of the College of Medical Evangelists. Among the autopsy protocols of the Los Angeles General Hospital we were able to find records of 36 cases of coccidioidal granuloma. In 9 of these, or 25 per cent, there was intracranial involvement. In 1 case a similar condition was observed at operation, but permission could not be obtained for autopsy. An additional case is reported through the courtesy of Dr. G. Wendell Olson and Dr. Dorrell G. Dickerson.

Since the disease was first described by Posadas,[1] numerous cases of coccidioidal granuloma have been reported in the literature. Most observers are fairly well agreed as to the morphologic and cultural

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1. Posadas: Rev. de chir. **21**:277, 1900. The same case had been reported in 1892 by Wernicke (Centralbl. f. Bakt. **12**:859, 1892).

characteristics of the organism Coccidioides immitis, which was so named by Rixford and Gilchrist.[2] As seen in the tissues, the parasite is a spherical body from 5 to 50 microns in diameter. Multiplication in infected tissues is accomplished by the development of small daughter parasites within the body of the parent organism, the cell wall of which later ruptures and allows them to escape. On artificial mediums the organism grows as a mold. While in some cases there is doubt as to the original atrium of infection, it seems definite that either the lungs or the skin may be the site of the primary infection. When the organism is lodged in the tissues it provokes the development of exudate, tubercle-like foci and granulation tissue. Probably the greatest difference from tuberculosis is the tendency to liquefaction necrosis rather than to caseation. From the original focus organisms gain entrance to

TABLE 1.—*Reported Cases of Coccidioidal Infection of the Central Nervous System*

Author	No. of Cases
Ophuls, W.: J. Exper. Med. **6**: 443, 1905	2
Evans, Newton: J. Infect. Dis. **6**: 523, 1909	1
Ryfkogel, H. A. L.: J. A. M. A. **55**: 1730, 1910	1
Brown, P. K., and Cummins, W. T.: Arch. Int. Med **15**: 608, 1915	1
Dickson, E. C.: Arch. Int. Med. **16**: 1028, 1915	1
Hammack, R. W., and Lacy, J. M.: California & West. Med. **22**: 224, 1924	1
Morris, Myrl: California & West. Med. **22**: 483, 1924	1
Jacobson, H. P.*: California & West. Med. **29**: 392, 1928	2
Evans, Newton, and Ball, H. A.*: J. A. M. A. **93**: 1881, 1929	3
Rand, Carl W.: Arch. Neurol. & Psychiat. **23**: 502, 1930	2
Beck, M. Dorothy: California Department of Public Health, Bull. 57, 1931	6
Davis, R. G.: U. S. Nav. M. Bull. **30**: 519, 1932	1
Sorsky, Eliot, and Nixon, C.: California & West. Med. **42**: 98, 1935	1

* These cases are included in our review.

the blood stream and are carried to other parts of the body to set up metastatic foci in various organs. Bones are often involved.

It has long been known that the nervous system and particularly its envelops may become infected. Since we are concerned in this contribution primarily with lesions of the nervous system, we have briefly tabulated the reported cases in which there was involvement of this system (table 1). In these cases meningitis was usually most pronounced about the base of the brain, but in the cases reported by Rand the spinal cord was involved. Beck was able to find 286 cases of coccidioidal granuloma reported from California prior to June 1, 1931. Those of our cases occurring before that date are included in her tabulation. Intracranial lesions were said to be present in 18 of her 286 cases. Six of her cases are not included in other reports noted in table 1 or in our series.

2. Rixford and Gilchrist: Johns Hopkins Hosp. Rep. **1**:211, 1896.

GENERALIZED COCCIDIOIDAL INFECTION WITH CRANIAL AND INTRACRANIAL INVOLVEMENT

As previously stated, in 25 per cent of cases of systemic coccidioidal infection in which autopsy was performed in the Los Angeles General Hospital there was intracranial involvement. We have summarized in table 2 the observations in 7 cases of generalized coccidioidal infection with intracranial involvement which we have studied. More detailed description of the intracranial pathologic process caused by Coccidioides immitis will be given in connection with the discussion of 7 other cases in which meningitis was unassociated with generalized infection.

PRIMARY CHRONIC COCCIDIOIDAL MENINGITIS

While cases of coccidioidal meningitis in which the meningitis is a part of the generalized coccidioidal infection are of much interest since they demonstrate the complexity of the clinical picture in certain instances, we feel that the cases of so-called primary chronic coccidioidal meningitis are of greater importance since the condition is likely to be confused with meningitis of other etiology. In these cases the first or primary clinical indication of coccidioidal infection is in the meninges, although the portal of entry into the body is elsewhere. The following group of 7 cases which we have studied seem to us to be examples of this primary type of lesion.

REPORT OF CASES

CASE 8.—A Mexican laborer, aged 60, a patient of Dr. F. F. Abbott of Ontario, Calif., died after an acute exacerbation of what was thought to be meningovascular syphilis. He had had headache, pain in the legs and cough for three months. The Wassermann reaction was positive. The white blood cell count was 15,600, with 86 per cent neutrophils. The spinal fluid pressure was increased, and there were 58 cells per cubic millimeter.

Autopsy.—The dura was adherent to the skull. There was an increase of cerebrospinal fluid. Meningeal exudate tending toward a fibrinous type was most marked at the base of the brain. There was marked engorgement of the vessels of the meninges. Lymphocytes, epithelioid cells, giant cells (Langhans' type) and C. immitis were present in the thickened leptomeninges. Two other small coccidioidal lesions were found. One was in the right lung and was well walled off. The other was in the spleen. Advanced syphilitic aortitis was also present.

CASE 9.—A Negro, aged 55, a gardener, was admitted to the Los Angeles General Hospital in a state of coma due to progressive chronic meningitis of about a year's duration. He had had headaches, stiff neck and nausea. The spinal fluid pressure was increased; the cell count was 140 per cubic millimeter. He died five days later.

Autopsy.—The vessels over the brain were congested. The pia-arachnoid was thickened at the base and less so over the hemispheres. There were no apparent tubercles, but in one area the thickened pia-arachnoid had the appearance of a whitish exudate. No lesions due to C. immitis were found within the brain or in

TABLE 2.—*Observations in Seven Cases of Generalized Coccidioidal Infection with Cranial and Intracranial Lesions*

Case	Race	Sex*	Age	Probable Primary Focus	Duration of Coccidioidal Infection	Duration of Meningeal Symptoms	Spinal Fluid Findings	Skull and Dura	Leptomeninges	Brain
Cranial Osteomyelitis, Epidural Abscesses and Associated Leptomeningitis										
1	Chinese	♂	40	Lungs	1 yr.	About 1 mo.	Cloudy fluid in ventricles†	Three epidural abscesses with osteomyelitis of skull	Thickened at base; small nodules along course of vessels	Normal
2	White	♂	31	Lungs	4½ mos.	15 days(?)	Normal†	Small epidural abscesses with osteomyelitis	Slight hyperemia at site of epidural abscesses	Normal
Coccidioidal Leptomeningitis (Only)										
3	Mexican	♂	43	Lungs (?), knee and joints (?)	4 mos.	3 mos.	1,188 cells, mostly lymphocytes; culture and smears negative	No lesions detected	Many small nodules about brain stem and sylvian fissure	Normal
4	Mexican	♀	21	Lungs (?)	1 yr.	About 2 mos.	No record	No lesions detected	Leptomeningitis present	Normal
5	White	♂	57	Lungs	7½ mos.	1 mo.	Pressure, 250 mm.; globulin, 2+; cells, 50 per cu. mm. smears and cultures negative	No lesions detected	Arachnoid thickened base; plaquelike tubercles over dorsolateral surface	Normal
Cases Presenting Subcortical Lesions Containing Coccidioides										
6	Mexican	♂	3	Skin over right frontal bone	6 mos.	2 mos.	Turbid fluid† over surface of brain but clear in ventricles	Adherent calvarium; erosion of outer table of right frontal and posterior part of left parietal bones	Marked pial congestion	Small nodule in right hemisphere; generalized edema
7	Filipino	♂	31	Lungs	5 mos.	Several days	Normal †	No lesion detected	Apparently normal	4 mm. nodule in right optic thalamus

* ♂ indicates males and ♀, female.
† Postmortem appearance.

the skull or elsewhere in the body. Sections of the meninges showed chronic meningitis, and numerous spores of C. immitis were present.

CASE 10.—A white man, aged 28, an oil worker, entered the Los Angeles General Hospital with the complaints of headache, vomiting and diplopia. It was thought that his illness was due to either an intracranial neoplasm or chronic meningitis. Ventriculography and examination of the spinal fluid failed to aid in the diagnosis. The patient died about four months after the onset of the symptoms.

Autopsy.—The convolutions of the brain were markedly flattened, and the vessels were congested. There were several minute patches scattered over the external surface which resembled miliary tubercles; these were seen particularly along the course of the middle meningeal artery. At the base the arachnoid was thickened and opaque. A cheesy, white exudate was present throughout the entire area. The ventricles were moderately distended, and the fluid was clear. The brain substance was essentially normal. Sections of the meninges revealed chronic coccidioidal meningitis with many of the parasites present. Coccidioides were also present in lesions over the right tibia and in the lungs and spleen.

CASE 11.—A Jugoslavian waiter, aged 38, entered the White Memorial Hospital on Oct. 22, 1925, in an unconscious state. His illness was of two months' duration. His chief complaint had been headache. A tumor of the brain was suspected, but an exploratory operation failed to confirm this, and he died on October 31. However, an antemortem culture taken from his nose revealed C. immitis. The spinal fluid pressure was 275 mm. of water. The fluid contained 952 cells per cubic millimeter.

Autopsy.—The meninges were markedly congested, and the ventricles were all greatly dilated and contained slightly cloudy fluid. At the base there were two foci of infection and localized thickening of the meninges. One of these covered about one half of the pons and extended down to the medulla. The other focus was farther forward and involved a fissure between the temporal and the frontal lobe for a short distance. The posterior clinoid processes and the floor of the sella turcica were extensively eroded, resulting in a direct communication with the nasal cavity, from which the infection may have been transmitted to the meninges. Sections taken from the granulomatous lesions revealed a chronic coccidioidal meningitis including the presence of many coccidioides.

CASE 12.—A Dutchman, aged 21, a bakery goods deliveryman, entered the Los Angeles General Hospital in May 1931 and was discharged on June 20, after receiving treatment for sinusitis, a furuncle in the external auditory canal and persistent headache. He was readmitted on October 20, because of severe headaches and disturbance of vision. He died on January 11, after suboccipital exploratory operation. At the time of the operation a piece of the arachnoid which showed patchy opacities was removed from the cisterna magna. Permission for autopsy was not granted. The sections of the arachnoid were characteristic of coccidioidal granuloma of the meninges.

CASE 13.—An oil worker, aged 34, was first seen by a physician on April 2, 1934. Occipital headache, pain in the neck and vomiting had been present five days. On and after May 13 there was an eosinophil count of from 10 to 15 per cent in the spinal fluid, along with an increase in the pressure. The total cell count was 350. Ventriculography in September failed to show any change in the intracranial structures. On December 17 an exploratory operation was performed in the right parietal region in the hope of finding a tumor in the frontal lobe, but none could be found. The patient died the following day.

Autopsy (Dr. Montanus).—The convolutions of the brain were somewhat flattened, and the sulci were shallower than normal. The vessels over the dorsolateral surfaces and at the base of the brain showed a marked degree of congestion, with accompanying marked edema of the subarachnoid space. At the base of the brain, confined entirely to the region of the optic chiasm, pons and medulla and approximately 3 cm. of the spinal cord there was a layer of gray-white, stringy, friable and apparently partially organized tenacious exudate, the thickness of which varied from 2 to 3 mm. The brain tissue was apparently normal, as were the ependyma and the choroid plexuses. The lateral ventricles were slightly dilated and contained clear fluid. No other lesions due to coccidioides were found in the body.

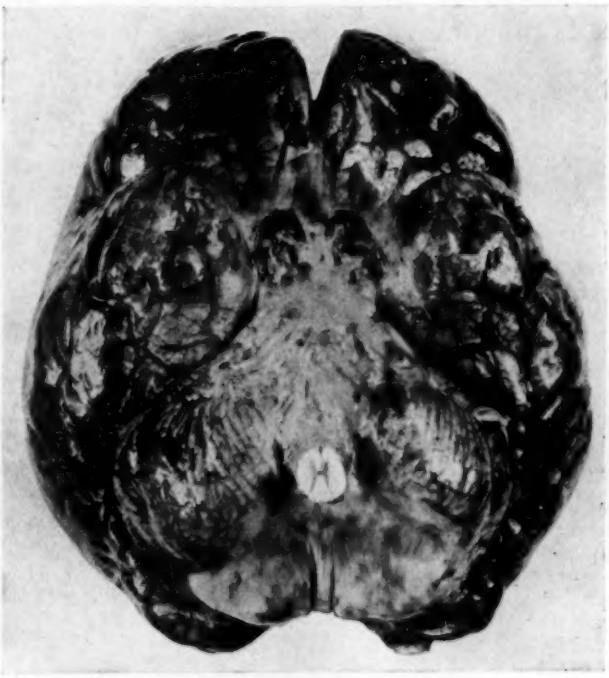

Fig. 1.—Base of the brain, showing marked thickening of the meninges by coccidioidal granuloma with pus distending the cisterna magna.

Sections and preparations stained with a solution of sodium hydroxide revealed the presence of C. immitis in the basilar exudate and meninges.

Case 14.—A Negro, aged 34, a laborer who had worked with raw cotton, entered the Los Angeles General Hospital on Oct. 29, 1934, in a stuporous mental state of twenty-four hours' duration and died of acute meningitis in thirty hours. Streptococci were found in the spinal fluid.

Autopsy.—The patient had had streptococcic septicemia, the original focus of infection probably having been acute sphenoid sinusitis. Aside from the intracranial changes, there were found bronchopneumonia, multiple abscesses in the kidneys, adhesive pericarditis and coccidioidal endocarditis.

The dura was normal in thickness but was diminished in luster and hyperemic. The leptomeninges were typical of streptococcic meningitis; the cisterna magna was markedly distended, forming a cystlike cavity which was filled with a yellow purulent material. The ventricles were dilated and filled with a heavy purulent exudate obscuring the choroid plexus. It was not suspected that the streptococcic meningitis was superimposed on a coccidioidal meningitis until sections were examined microscopically. The leptomeninges were thickened, and the interstitial spaces were infiltrated with polymorphonuclear leukocytes. In the partially organized exudate a number of coccidioidal parasites were contained in giant cells.

PATHOLOGIC PROCESS

From a study of the 14 cases reported here and from a review of the literature, it appears that the cranial and intracranial lesions of coc-

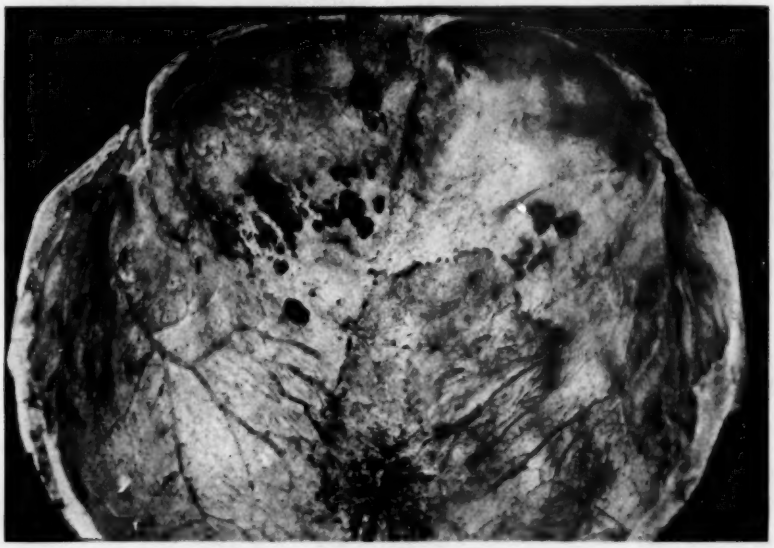

Fig. 2.—Inner surface of the skull, showing erosion by osteomyelitis associated with coccidioidal meningitis.

cidioidal granuloma may be divided into two groups: (1) those that are associated with a systemic infection and (2) those that are primary in the sense that symptoms of involvement of the central nervous system are the most outspoken ones and that the original focus of infection is not evident. While infection does not actually begin in the meninges but is secondary to a focus in the skin or lungs, it was found that the original foci may show remarkable degrees of healing, such as was seen in case 8. In 4 cases (cases 9, 11, 12 and 13) no coccidioidal lesions outside of the cranium were found, but it is our opinion that the lesion at the portal of entry was minute and had probably healed so completely that it was not observed at autopsy. The portal of entry

in case 11 was most probably the sinuses; thus it is evident that the meningitis in these cases of so-called primary meningitis is secondary to pulmonary lesions, infection of the accessory sinuses or cutaneous lesions.

Leptomeningitis is the most important intracranial lesion caused by coccidioidal granuloma. The meningeal lesion is a chronic inflammatory process which appears in three characteristic forms. The first form

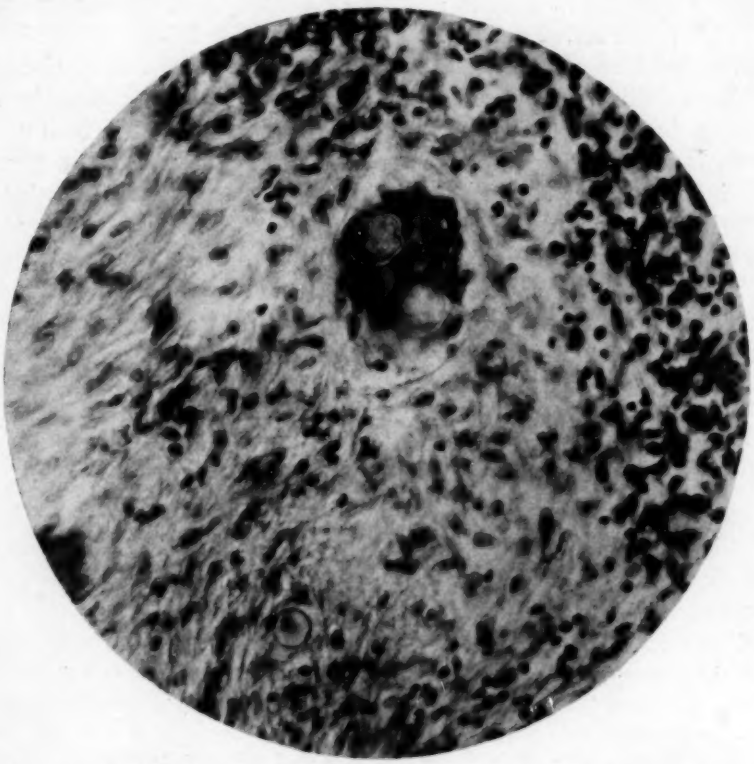

Fig. 3.—Photomicrograph showing C. immitis. Two of the organisms are seen within a giant cell. Magnification, × 680.

consists of nodules, which are small, more or less rounded or irregular, frequently flattened lesions varying in size from that of a millet seed to that of a pinhead. These tend to follow the course of the vessels and are distributed over the dorsolateral surfaces and at the base of the brain. Microscopically the lesions are practically identical with those caused by tubercle bacilli, except that coccidioides are present. The second form consists of larger, irregular plaquelike patches of exudate which occur in the spinal meninges and in the basilar cisterns.

These plaques may vary from 0.5 to 2.5 cm. in diameter. They can be distinguished both macroscopically and microscopically from the tubercles caused by acid-fast bacilli. These accumulations are composed of both cellular exudate and granulation tissue (case 12). The lesions may present a condensation of collagen fibers, as was described by Basgal and de Azevedeo [3] in their sections of the spinal meninges. Morris also described a plaque in the cerebral leptomeninges of his patient. The third form consists of thick accumulations of plastic exudate. These are usually in the basilar cisterns, but it is likely that the exudate may also involve the spinal meninges. We have observed that this exudative reaction has been more extensive and more common in acute coccidioidal meningitis which accompanies the generalized infection than in the primary chronic meningitis, although it has been observed in both types. Fibrin is often abundant. Neutrophils are frequently more numerous than in tuberculous exudate. It has also been our observation that in most instances the meninges in all of these three types show more scarring than is ordinarily seen in tuberculous meningitis.

There is usually a marked congestion of the pial vessels, and the convolutions show a variable degree of flattening, depending on the reaction of the cortex and the extent of ventricular dilatation.

In our cases of primary chronic meningitis no coccidioidal lesions of the cerebral tissues were found, while in the group with generalized systemic infection subcortical lesions were observed in 2 cases.

In 4 cases of primary chronic meningitis the brain showed moderate to marked dilatation of the ventricles, and there was clinical evidence of at least a moderate degree of hydrocephalus in case 12. The hydrocephalus appeared to be the obstructive type, being secondary to an obstruction of the basilar foramina by exudate.

The cranial and intracranial lesions associated with systemic infections in our series may be subdivided into three subgroups: (1) cranial osteomyelitis [4] with associated abscesses and meningitis or meningismus

3. de Azevedo, A.: Compt. rend. Soc. de biol. **109**:125, 1932.

4. Coccidioidal osteomyelitis of the skull resembles the destructive lesions of other bones which are characteristic of the infection. The lesions we have seen have all occurred as small round or oval punched-out areas in one or both tables of the skull. These may be divided into two general groups: 1. Those entering the external surface of the skull are associated with subaponeurotic lesions of the outer table of the skull. Organisms appear to be carried to the foci by the blood stream, from the lungs or other infected areas. All degrees of depth of erosion of the skull have been present. 2. The other group of lesions are intracranial in origin. In some of the specimens we believe that the organisms have followed the venules through the inner table, attacking it, and then on into the diploe, spreading more extensively in these spaces. Others showed many small foci of necrosis grouped together, each one measuring from 0.5 to 2 or 3 mm. in

(Footnote continued on next page)

(cases 1 and 2), (2) leptomeningitis with no other cranial or intracranial lesions (cases 3, 4 and 5) and (3) subcortical lesions [5] (cases 6 and 7).

SUMMARY

Infection of the leptomeninges by C. immitis occurs in about one fourth of the cases of coccidioidal granuloma.

Meningeal infection assumes one of two forms. It occurs either as acute meningitis following a generalized infection or as chronic meningitis of the so-called primary type. The latter is so designated because the meningeal symptoms signalize the onset of the disease. In this study 14 cases of coccidioidal meningitis have been studied, 7 of the acute and 7 of the chronic type.

In the primary form the clinical symptoms are essentially those of chronic meningitis, at times with additional manifestations indicative of obstructive hydrocephalus. The disease cannot be excluded on the basis of findings in the spinal fluid. The pressure of the fluid is practically always increased. In most instances no organisms can be isolated from the fluid either on smear or on culture. Organisms have been found in the fluid at times after surgical intervention when they were not found before. The cell counts in our cases varied from 58 to 2,000 per cubic millimeter. Lymphocytes averaged 75 per cent of the cells and neutrophils 25 per cent. Eosinophilia in the spinal fluid was noted in 1 of our cases. In 1 case of generalized coccidioidal infection the organisms were found in blood smears and cultures. There is usually a moderate leukocytosis with a relative increase of neutrophils in the blood. Slight fever is ordinarily present.

The meningeal lesion may be in one of three forms: (1) numerous small flattened tubercles, usually predominant over the dorsolateral surfaces of the brain, (2) larger, plaquelike patches of exudate and granulation tissue, which may be found in the basilar cisterns, and (3) thick

diameter. As a rule these did not perforate the inner table but affected it superficially. Erosion of the sella turcica with loss of its floor and involvement of the posterior clinoid processes with a direct communication into the sphenoid sinus and the nasal cavity was the only instance of cranial osteomyelitis in the group of cases of so-called primary meningitis, but table 2 shows that meningitis and cranial osteomyelitis are rather frequently associated.

5. In case 6 the brain presented a subcortical nodule in the right hemisphere which was a collection of tubercles similar in every respect to the tubercles caused by acid-fast bacilli except that coccidioides were present. In the center was caseous material surrounded by round cells, epithelioid cells and proliferated glial cells. The glia cells were not abundant, but there was evidence of an attempt on the part of the body to wall off the process. Giant cells with coccidioides in them were present. The brain tissue surrounding the nodule was congested, and there was round cell infiltration around the blood vessels. The histopathologic picture of the lesion in the optic thalamus in case 7 was identical with that in case 6.

accumulations of plastic exudate, which are usually confined to the basilar cisterns though they may occur also about the spinal cord. Frank pus seems to be uncommon in the chronic form. Obstructive internal hydrocephalus is the rule in the chronic form and occurs in about half the cases in the acute form. Lesions of the brain itself are extremely rare in cases of chronic meningitis but probably occur in about 25 per cent of the cases of the acute form.

Coccidioidal osteomyelitis of the bones of the vault or the base of the brain or of the vertebrae may accompany the acute form of the disease. In but 1 case of primary chronic coccidioidal meningitis was bony involvement found. Roentgenograms of the skull may disclose typical erosion, and this may be of help in arriving at a diagnosis in obscure cases.

MORPHOLOGIC ASPECTS OF THE LOCAL SHWARTZMAN PHENOMENON

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Since the original description by Shwartzman [1] of the phenomenon of local reactivity to bacterial filtrates, a number of immunologic and morphologic investigations have been undertaken with a view to establishing its place in the category of immune processes. Morphologic similarities between the Shwartzman phenomenon and other immunologic manifestations have led to attempts to identify it with such conditions as the Arthus phenomenon, bacterial allergy and others. In extensive experiments on the phenomenon, Shwartzman [2] pointed out the striking differences that exist between this entity and other immunologic conditions.

Previous histologic studies of the phenomenon were reported by Apitz,[3] Kielanowski and Selzer [4] and Karsner and Moritz.[5] The present investigation concerns itself with the histologic changes attendant on the production of the Shwartzman phenomenon in the skin of rabbits. An analysis of the morphologic changes is made, with a view to contributing to a clearer understanding of this new immunologic entity.

MATERIAL AND METHODS

Rabbits were used in all the experiments. An area of skin of the abdomen was epilated, and the animals were not used until the following day in order to permit any local irritation caused by the depilatory to subside. Sections of skin used as controls showed no evidence of inflammation. The bacterial filtrates employed for the first injection, which was always administered intradermally, are termed preparatory factors. The intradermal injection of the filtrate is termed the skin prepa-

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1. Shwartzman, G.: Proc. Soc. Exper. Biol. & Med. **25**:560, 1928; J. Exper. Med. **48**:247, 1928.

2. Shwartzman, G.: J. Exper. Med. **51**:571, 1930.

3. Apitz, K.: Ztschr. f. d. ges. exper. Med. **89**:699, 1933.

4. Kielanowski, T., and Selzer, A.: Bull. internat. Acad. polon. d. sc. et d. lett., Cl. méd., 1934, p. 417.

5. Karsner, H. T., and Moritz, A R.: J. Exper. Med. **60**:37, 1934.

ration. The second injection was given intravenously, usually twenty-four hours after skin preparation. Bacterial filtrates used for intravenous injection are spoken of as reacting factors. All the filtrates were prepared in the manner described by Shwartzman.[6]

The filtrates used for intravenous administration were titrated for reacting potency against a constant skin-preparatory dose, and the dose is expressed in terms of reacting units.[7] In some instances various dilutions of filtrate employed for skin preparation were tested against a constant dose of reacting factors, as indicated in the following typical experiment:

Each group of three rabbits received a single intradermal injection of filtrate of agar washings of cultures of typhoid bacilli in dilutions ranging from 1:5 to 1:300. Twenty-four hours later all the rabbits received 5 reacting units (i. e., a dilution of 1:60) of the same filtrate intravenously. Positive reactions were obtained in sites prepared with dilutions ranging from 1:5 to 1:200. No reactions were obtained in sites prepared with higher dilutions. Although each batch of filtrate employed was not tested in this manner, it may be stated safely that most of the filtrates of the same strain of organism used in this laboratory possess a similar skin-preparatory range.

The site of the reaction and a large area of surrounding normal skin were removed in each instance. Care was taken to include the entire thickness of the abdominal wall, since in many instances the reaction extended into the muscular layers. Sections of the skin site were fixed simultaneously in a dilute solution of neutral formaldehyde U. S. P. (1:10), Zenker's fluid and 95 per cent alcohol. The hematoxylin and eosin, fibrin, Giemsa, Van Gieson and elastic tissue stains were used.

The results of the experiments and of the corresponding histologic studies are reported under the following heads:

Shwartzman phenomenon

- Group A: Skin preparation
- Group B: The typical phenomenon
- Group C: Relationship between skin preparation and the phenomenon
- Group D: Skin preparation with a nonphenomenon-producing substance
- Group E: Elicitation of the phenomenon with a bacterial filtrate of low potency
- Group F: Skin preparation followed by a second intradermal injection of bacterial filtrate into the same site

Arthus phenomenon

SHWARTZMAN PHENOMENON

Group A: Skin Preparation.—Control Experiments: In the preparation of the bacterial filtrates a number of substances of nonbacterial nature are necessarily introduced. A final step in the preparation of the filtrates consists of washing cultures of the organism on plain or dextrose agar in Kolle flasks with a 0.4 per cent phenolized saline solution. The washings, after centrifugation, are passed through a Berkefeld filter, and the necessary further dilutions are made with 0.85 per cent sterile saline solution. It was decided, therefore, to investigate the rôle that the diluent may play in the production of inflammatory changes. The

6. Shwartzman, G.: Proc. Soc. Exper. Biol. & Med. **26**:843, 1929; J. Infect. Dis. **45**:232, 1929.

7. Shwartzman, G.: J. Exper. Med. **52**:781, 1930.

surface of sterile, plain and dextrose agar in Kolle flasks was washed with a 0.4 per cent phenolized saline solution; the washings were passed through a Berkefeld filter, and 0.25 cc. of the filtrate was injected intradermally into four rabbits. Two animals were killed at the end of six hours and the others at the end of eighteen hours. The site of injection presented a small erythematous wheal, about 0.5 cm. in diameter, which became larger and edematous at the end of six hours. At the end of eighteen hours the erythema and edema had subsided. Histologic sections of the skin six hours after injection showed moderate edema of the subcutis, with focal accumulations of polymorphonuclear leukocytes and capillary congestion. The cells were often grouped about small vessels. Sections of the skin eighteen hours after injection presented a small area of necrosis of the epithelium and corium at the site of penetration of the needle. Beneath this area was a focal cellular infiltration consisting chiefly of polymorphonuclear leukocytes. Many of these cells showed degenerative changes. Occasional histiocytes were present. Capillary congestion was still notable, whereas the edema had disappeared. No thrombosis or other vascular alterations were observed. The inflammation was limited to the corium and the upper layers of the subcutaneous tissues, in no instance extending to the muscle. The phenolized saline washings of dextrose agar produced a greater degree of inflammation than those of plain agar.

It is thus evident that substances employed in the preparation and dilution of bacterial filtrates may contribute in some degree to the inflammation that follows skin preparation. The significance of this observation will be discussed subsequently.

Skin Preparation: In order to determine the effect of skin preparation alone, a series of eight rabbits were given intradermal injections of 0.25 cc. of a filtrate of typhoid bacilli, in a dilution of 1:4. The animals were killed at intervals of six, eighteen, twenty-four, forty-eight, seventy-two, ninety-six, one hundred and twenty and one hundred and sixty-eight hours subsequent to intradermal injection.

Grossly, the prepared site six hours after intradermal injection showed slight edema and erythema involving an area measuring about 1 by 1.5 cm. The site was sharply demarcated from the surrounding normal skin. At the end of eighteen hours the edema had receded, although erythema still persisted. At the end of twenty-four hours the skin site was of normal appearance. The injected area was marked off with a ring of trinitrophenol in order to permit differentiation from the surrounding normal skin.

Sections of skin taken six hours after injection of the filtrate showed diffuse infiltration of polymorphonuclear leukocytes that extended from the corium through the subcutaneous tissue to the fascia. Frequently the cells were accumulated about veins and occasionally about arteries. There was pronounced edema of the subcutis, with moderate swelling of the collagen fibers. The capillaries and venules were dilated and filled with erythrocytes and a few leukocytes. Occasionally small foci of hemorrhage were noted in the subcutis. Sections of the prepared site at the end of eighteen hours presented a less degree of edema, with, however, intensification of the leukocytic infiltration (fig. 1). The cellular infiltration at times extended through the fascia into the upper layer of muscle. The lymphatics were dilated and contained many degenerated leukocytes. The foci of hemorrhage were but slightly increased in extent. All the blood vessels were surrounded by collars of leukocytes, and the walls of occasional veins showed infiltration. In twenty-four hours the inflammation had reached its peak. The vascular congestion was less striking. Many leukocytes were in the process of disintegration. Histiocytes, lymphocytes and occasional plasma cells were now evident. There was proliferation of the fixed histiocytes; these cells were large, with

abundant basophilic cytoplasm, and contained large, lobate, dark-staining nuclei. No significant epithelial changes were present. At the end of forty-eight hours there was decided diminution of the cellular infiltration, and edema was no longer evident. Small foci of necrosis, containing disintegrated leukocytes, were scattered in the subcutaneous tissues. There was early fibroplastic proliferation about these foci. At the end of seventy-two hours only occasional inflammatory cells were seen. Later sections showed complete replacement of the necrotic foci by connective tissue. Total subsidence of the inflammatory reaction occurred within five days after skin preparation. The vessels presented no residual changes. Thrombosis was not observed. With the Giemsa stain the leukocytes were identified as pseudo-eosinophils. No true eosinophils were present in significant numbers.

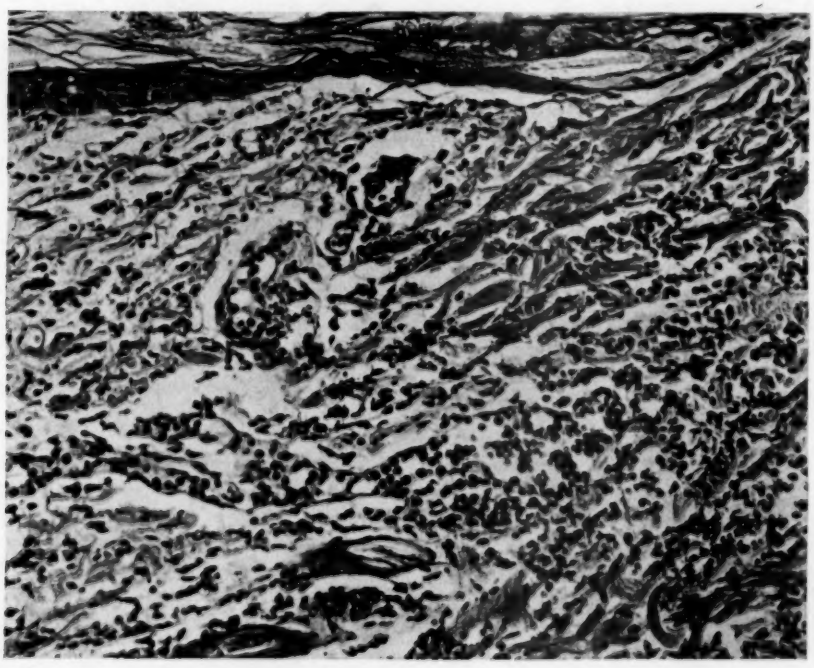

Fig. 1 (group A).—Section of the skin site eighteen hours after the intradermal injection of 0.25 cc. of typhoid bacillus filtrate in a dilution of 1 : 4, showing diffuse infiltration of polymorphonuclear leukocytes, edema and dilatation and congestion of the vessels.

Skin preparation with bacterial filtrates, therefore, gives rise to a moderate degree of inflammation, which is characterized by rapidly developing edema, capillary and venous congestion and diffuse infiltration with polymorphonuclear leukocytes. The inflammation reaches a peak within twenty-four hours and then begins to recede. Small foci of necrosis are observed in the subcutaneous tissues. Within from forty-eight to seventy-two hours the inflammation tends to subside completely. At no time is thrombosis or other significant vascular alterations observed.

Group B: The Typical Phenomenon.—The phenomenon was produced in twenty-one rabbits. The animals were divided into two groups. One group, consisting of twelve rabbits, received an intradermal injection of 0.25 cc. of a meningococcus filtrate in a dilution of 1:2, followed in twenty-four hours by the intravenous administration of 50 reacting units of the same filtrate. The animals were killed at the following intervals after intravenous injection: ten minutes, thirty minutes, one hour, one and three-fourths hours, two and one-half hours and three and one-fourth hours. The second group, consisting of nine rabbits, received 0.25 cc. of undiluted typhoid bacillus filtrate intradermally, followed twenty-four hours later by an intravenous injection of 50 reacting units of the same filtrate. The animals were killed at the following intervals after intravenous injection: four, twenty-four, seventy-two and one hundred and twenty hours and seven, ten, twelve, fourteen and twenty-eight days, respectively. The results for the combined groups present the morphologic picture of the phenomenon from ten minutes to twenty-eight days after intravenous injection.

In the first three animals, namely, those killed ten, thirty and sixty minutes after intravenous injection, no gross changes were shown at the prepared skin site. At the end of one hour there appeared a circumscribed area of edema, of pinkish hue, the edges of which merged gradually with the surrounding normal skin. In one and three-fourths hours there was increased swelling of the site, with the appearance of petechiae in the center of the edematous area. The hemorrhages gradually increased in size and number and tended to become confluent. The site was then deep purplish. The rapid increase of swelling extended to form an area about 4 cm. in diameter. The periphery of the reaction was deep red and rather sharply demarcated from the surrounding skin. At the end of four hours the hemorrhagic appearance was striking, and the swelling was so pronounced that the central portion of the reaction was elevated about 0.5 cm. above the surface of the normal skin. During the subsequent twenty-four hours there was little change. Later, the center became bluish-black and the skin dry and stiff, so that it could not be moved freely over the underlying tissues. At the end of forty-eight hours the edema had receded, and the involved skin formed a thick black hemorrhagic crust with sharply defined edges, surrounded by a rim of deep red skin. Within three to four days the central dry hemorrhagic crust began to separate at the edges, and by the seventh day it had fallen out, leaving a shallow defect the base of which consisted of young granulation tissue. Epitheliation of the defect required more than four weeks.

Histologic studies of the sections obtained ten and thirty minutes after injection of the reacting factors revealed no differences between these and the sections obtained after skin preparation alone, for the corresponding period (twenty-four hours). The earliest changes observed occurred in the skin removed one hour after intravenous injection. There was widespread dilatation of the capillaries and venules, which were filled with erythrocytes. Adjoining the capillaries, masses of extravasated erythrocytes lay between the connective tissue fibers. The hemorrhages were most numerous in the subepithelial layer and only later extended into the subcutaneous tissues. No significant endothelial changes were noted in the capillaries, veins or arteries. Only occasional ruptured capillaries were seen.

The area of cutaneous reaction one and three-fourths hours after injection of the reacting factors showed a moderate increase in the number and size of the hemorrhagic areas. In these areas, for the first time, thrombotic masses were observed in the small and medium-sized veins. The thrombi varied from small parietal clumps to large plugs that filled the entire lumen of the vessel. They

consisted of acidophilic amorphous material, within which were scattered degenerated leukocytes and erythrocytes. With the Weigert fibrin stain, scattered strands or clumps of fibrin were noted. These were present only on the surface of most of the thrombotic masses. However, in several instances the entire thrombus consisted of strands of fibrin with enmeshed leukocytes and red cells. The vessels which contained thrombi were surrounded by collars of polymorphonuclear leukocytes, and often the entire wall of a vessel was infiltrated with these cells. The vascular endothelium, however, was intact. In addition to the thrombi and the marked hemorrhage, there was generalized edema of the entire skin site, represented by the presence of homogeneous eosinophilic substance between the connective tissue fibers and about the vessels. The collagen fibers were swollen. A marked leukocytic infiltration extended from the corium to the fascia. A section of the skin site taken three and one-fourth hours after injection of the reacting factors showed extension of the inflammatory reaction, with infiltration of large groups of leukocytes between the muscle fibers and a striking increase in the extent of the hemorrhage (fig. 2). In many places hemorrhage into the papillae produced elevation of the overlying epithelium. There was, likewise, a decided increase in the extent of the thrombosis. Large masses of leukocytes, many showing advanced degenerative changes, were present in the subcutaneous tissues. All the vessels in the involved area were intimately surrounded by leukocytes. A section of the area of cutaneous reaction taken twenty-four hours after intravenous injection of the reacting factors showed many foci of necrosis in the subcutaneous tissue. These contained disintegrated leukocytes in great numbers. Many lymphocytes, macrophages and occasional plasma cells were noted. Early proliferation of the fixed histiocytes was observed at this time. In some of the veins endothelium covered the surface of the thrombus. Although many arteries and the majority of the veins were infiltrated by leukocytes, the elastica was intact in all the vessels. In one instance the wall of a large artery was necrosed, and the lumen was filled with a massive thrombus of fibrin. Many muscle fibers did not stain well, and others appeared waxy and swollen. In subsequent sections there was focal calcification of necrotic muscle fibers. Seventy-two hours after intravenous injection, a section of the area of cutaneous reaction showed regression of the inflammatory process. A number of vessels contained partially organized thrombi. In other instances there appeared to be diminution in the amount of vascular thrombosis without residual changes. Cells of the chronic inflammatory type were present in increasing numbers, particularly macrophages. The dry hemorrhagic crust, observed grossly, was seen to consist of a wide zone of necrotic epithelium and subjacent corium. Within the necrotic zone, consisting of nuclear and granular débris and shadows of erythrocytes, the outlines of necrosed vessels were still evident. The necrotic mass was surrounded by a wide zone of inflammatory cells, and at the periphery there was early fibroplastic proliferation. Subsequent sections showed organization of the necrotic foci in the subcutaneous tissues and growth of granulation tissue about the hemorrhagic superficial crust. The adjacent uninvolved epithelium showed evidences of proliferation. Sections of the skin site seven days after the appearance of the reaction showed an epithelial defect at the site previously occupied by the dry hemorrhagic crust. The edges consisted of proliferating epithelium, and the base, of young granulation tissue within which there were numerous macrophages, lymphocytes and plasma cells.

Summary: Histologically, the phenomenon presented the following tissue changes: severe capillary dilatation and engorgement of the vessels, foci of hemorrhage which rapidly increased in size and number until the entire area was involved, venous thrombosis, occasional arterial necrosis and thrombosis and severe inflam-

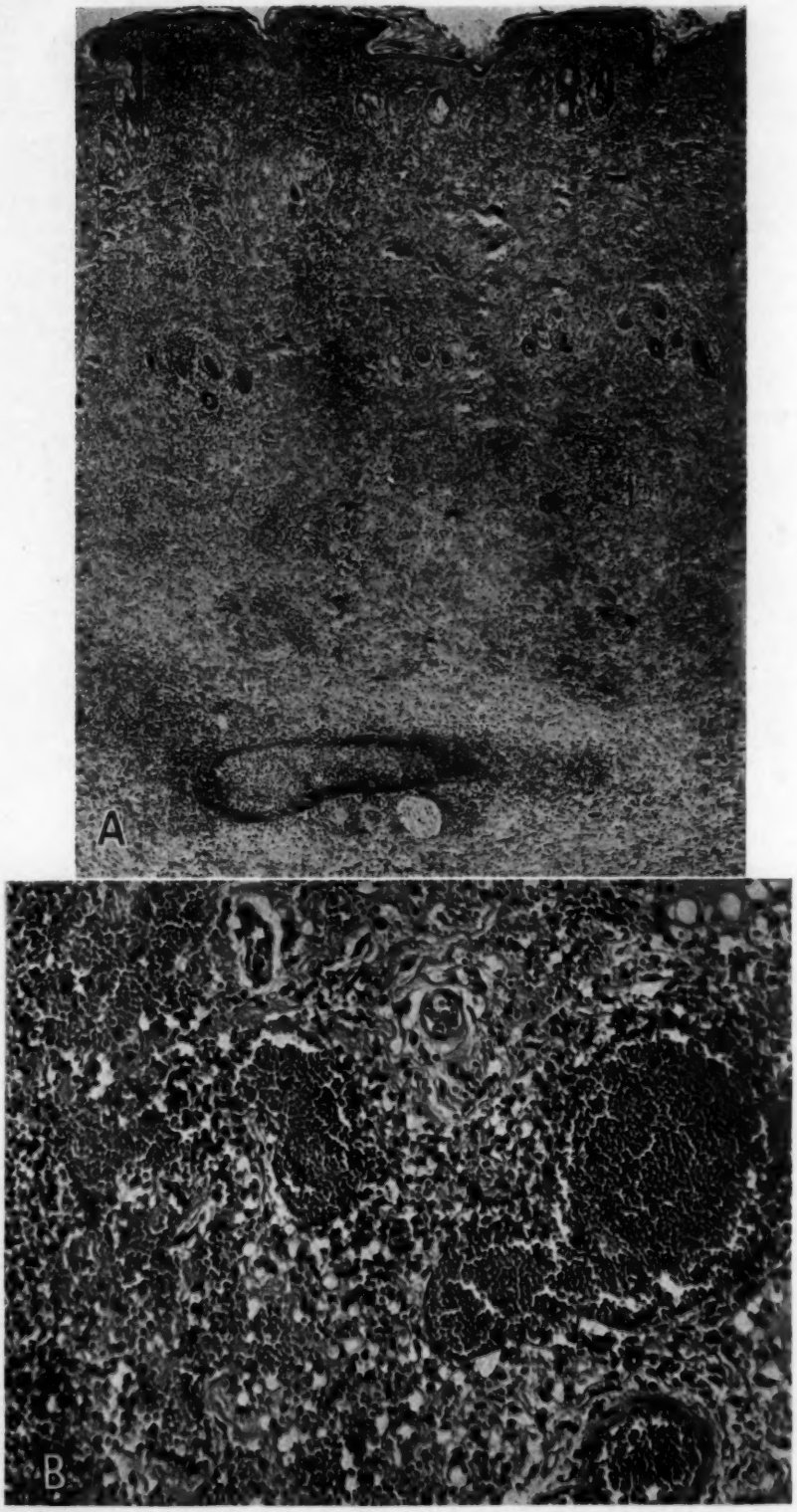

Fig. 2 (group B).—*A* is a section of skin photographed under low magnification, showing the fully developed phenomenon three and one-half hours after the intravenous injection of the reacting factors. There are marked inflammation, hemorrhage and thrombosis of the veins. *B* shows a higher magnification of the section shown in figure 2*A*, demonstrating extreme vascular engorgement and perivascular collars of leukocytes, with infiltration of the walls and extravasated erythrocytes between the connective tissue fibers.

mation. No significant endothelial alterations were observed. The changes first appeared about one hour after injection of the reacting factors and were striking within from three to four hours. Within the following twenty-four hours there was little change, except the appearance of foci of necrosis in the subcutaneous tissues. Subsequently, there were regression of the inflammation, necrosis of the overlying epithelium and corium, resorption of the hemorrhage, sloughing of the necrotic tissues and repair of the defect by granulation tissue. Some of the thrombi were organized. Epitheliation required more than four weeks.

Group C: Relationship Between Skin Preparation and the Phenomenon.—In order to ascertain whether any relationship existed between the histologic changes following skin preparation alone and those following the appearance of the phenomenon, reactions to the following tests were compared:

1. Bacterial filtrates possessing a very high skin preparatory potency were used.

2. Skin preparation was performed with a large dose of bacterial filtrate, and forty-eight hours elapsed before reacting factors were injected.

3. Skin preparation was performed with bacterial filtrate almost completely neutralized by homologous antitoxic horse serum and with nonneutralized filtrate, and the phenomenon was elicited in hoth instances.

1. A series of eight rabbits received intradermal injections of 0.25 cc. of typhoid bacillus filtrate in a dilution of 1:150. This filtrate possessed a very high degree of skin-preparatory potency as compared with other filtrates. The prepared skin sites were removed six, twenty-four, forty-eight and ninety-six hours later. No intravenous factors were injected. The prepared sites showed slight redness and swelling, which persisted for several hours. Histologically, there was seen six hours after intradermal preparation a moderate degree of edema of the subcutaneous tissues with discrete leukocytic infiltration beneath the epithelial pegs and in the subcutis between the collagen fibers (fig. 3*A*). There was also a slightly perivascular arrangement of the infiltrated cells. Only occasional dilated capillaries were present. The degree of inflammation observed was no greater than that obtained in the controls when phenolized saline washings of sterile plain or dextrose agar were injected intradermally. Within twenty-four hours the edema had subsided; the inflammatory reaction increased only slightly. Within forty-eight hours there was decided recession of the inflammatory reaction, so that only small scattered groups of disintegrating leukocytes were evident. Section of the skin ninety-six hours after intradermal preparation presented no evidences of inflammation.

Two additional rabbits with the skin of the abdomen prepared in a similar manner (typhoid bacillus filtrate in a dilution of 1:150) then received 25 reacting units of the same filtrate intravenously twenty-four hours after skin preparation. The phenomenon appeared within four hours and was characterized by swelling and hemorrhage at the prepared site. The reaction was about the size of a silver half-dollar and was sharply demarcated from the surrounding normal skin. Histologic sections presented changes similar to those described for the animals used in the studies of group B for the corresponding period, with the distinction that the hemorrhage was more pronounced than the inflammatory reaction (fig. 3*B*). Venous thrombosis was present to a similar degree. The leukocytic infiltration of the subcutis was less marked than that observed in the animals used in the studies of group B. All the other histologic features were identical in the two groups.

2. Two rabbits received 0.25 cc. of a meningococcus filtrate in a dilution of 1:10, intradermally. Forty-eight hours later the skin was removed for section. No factors were administered intravenously. The prepared sites presented a

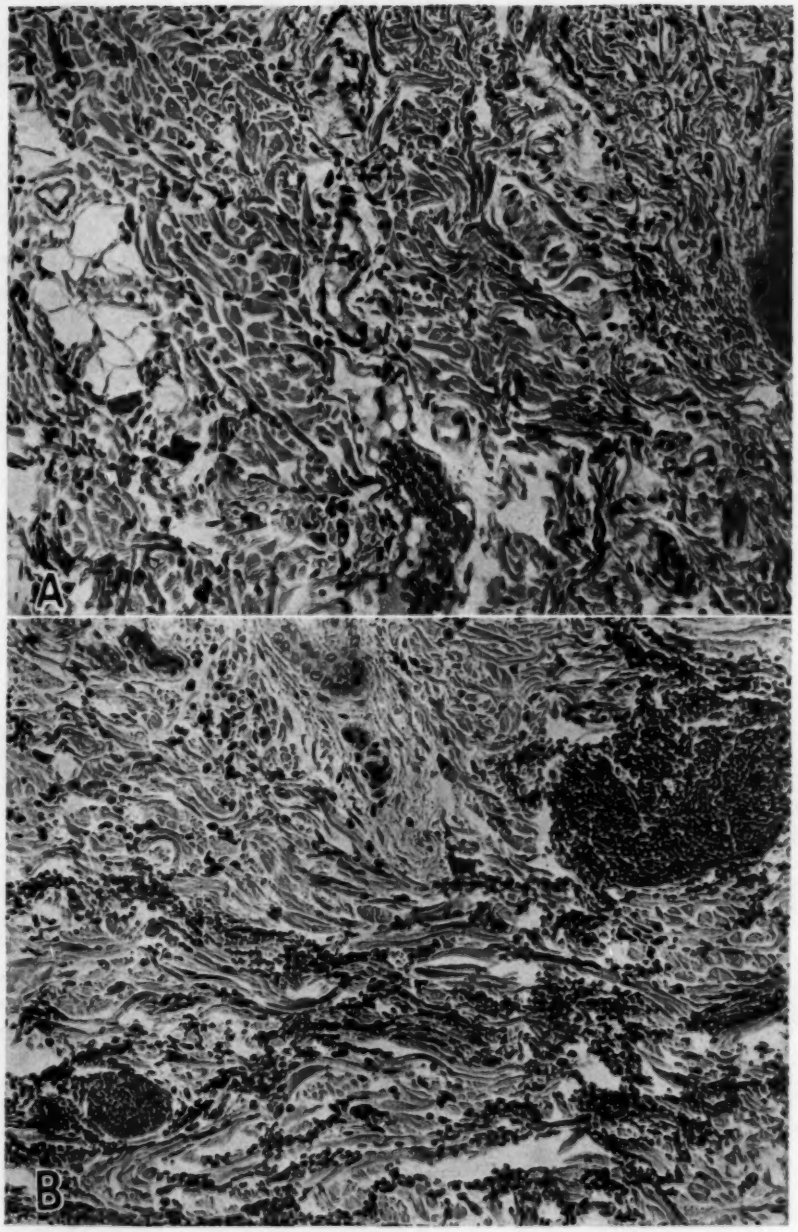

Fig. 3 (group C, subgroup 1).—*A* is a section of the skin site six hours after the intradermal injection of typhoid bacillus filtrate in a dilution of 1 : 150. There is only slight inflammation, with occasional dilatation of the vessels. *B* shows the histologic appearance of the typical phenomenon after skin preparation with typhoid bacillus filtrate in a dilution of 1 : 150, followed by intravenous injection of 25 reacting units of the same filtrate. The striking hemorrhage and vascular engorgement are evident.

moderate degree of redness and swelling for an area about 1.5 cm. in diameter. Within forty-eight hours this reaction had completely subsided, and only a faint pink remained to indicate the site of injection. Histologically, the sections of skin showed a severe degree of inflammation characterized by leukocytic infiltration, edema and perivascular infiltration. The cells were accumulated in dense groups and extended from the subepithelial tissues to the muscular layer. Thromboses and hemorrhages were not observed. Many of the capillaries were dilated.

A rabbit, with the skin of the abdomen prepared in a similar manner, was given 100 reacting units of a meningococcus filtrate intravenously forty-eight hours later, and the skin was removed four hours after injection of the reacting factors. Grossly, the typical skin phenomenon consisted of a swollen hemorrhagic area about 2.3 cm. in diameter, with incomplete demarcation from the surrounding normal skin. Histologically, the section was characterized by the presence of a severe degree of inflammation, more marked than that seen in the sections described in the preceding paragraph. There was, in addition, a striking degree of hemorrhage, which involved the entire thickness of the skin. Occasional ruptured capillaries were noted. The hemorrhage produced disruption of the collagen fibers of the subcutaneous tissue, surrounded the vessels and extended into the upper layers of the muscle. Numerous venous thromboses were evident.

A comparison of the sections taken from the prepared skin sites in which subsequent intravenous injections were made and those in which no intravenous injections were made indicated that the severe degree of inflammation present with skin preparation alone in this experiment in no way influenced the subsequent appearance of the phenomenon. In the instance in which an intravenous injection had been given, the inflammation was definitely more striking, and the hemorrhage and thrombosis were characteristic.

3. Two skin sites on the abdomen of each of two rabbits were prepared as follows: At one site was injected 15 units of typhoid bacillus filtrate admixed with one part of homologous antitoxic horse serum (sufficient to produce almost complete neutralization of the toxin). At the other site, was injected 15 units of typhoid bacillus filtrate mixed with one part of normal horse serum. Grossly, the prepared sites, at the end of twenty-four hours, showed only slight edema with faint pink coloration in an area about 1.5 cm. in diameter. Histologically, there was evident in both instances a moderate degree of inflammation consisting of infiltration of polymorphonuclear leukocytes, slight capillary dilatation and edema.

A rabbit with two skin sites on the abdomen prepared in a similar manner received at the end of twenty-four hours 25 reacting units of typhoid bacillus filtrate intravenously. Four hours later the skin sites were examined and removed. At the point of injection of the filtrate and homologous antitoxic serum there was observed only a slightly raised area, about 1.25 cm. in diameter, with a deep red center gradually fading into faint pink at the periphery. This would usually be classified as a 1 plus reaction. At the site of injection of the filtrate and normal horse serum there was a typical 4 plus reaction, with marked hemorrhage and swelling. Histologically, the skin site showing the 1 plus reaction presented a degree of inflammation only slightly in excess of that noted in the similarly prepared area in which no intravenous factors were administered (fig. 4 *A*). Only occasional thrombosis and slight hemorrhage were noted. The skin site prepared with nonneutralized filtrate in which the reaction was typically 4 plus presented a histologic picture like that described in instances of the typical phenomenon (fig. 4 *B*).

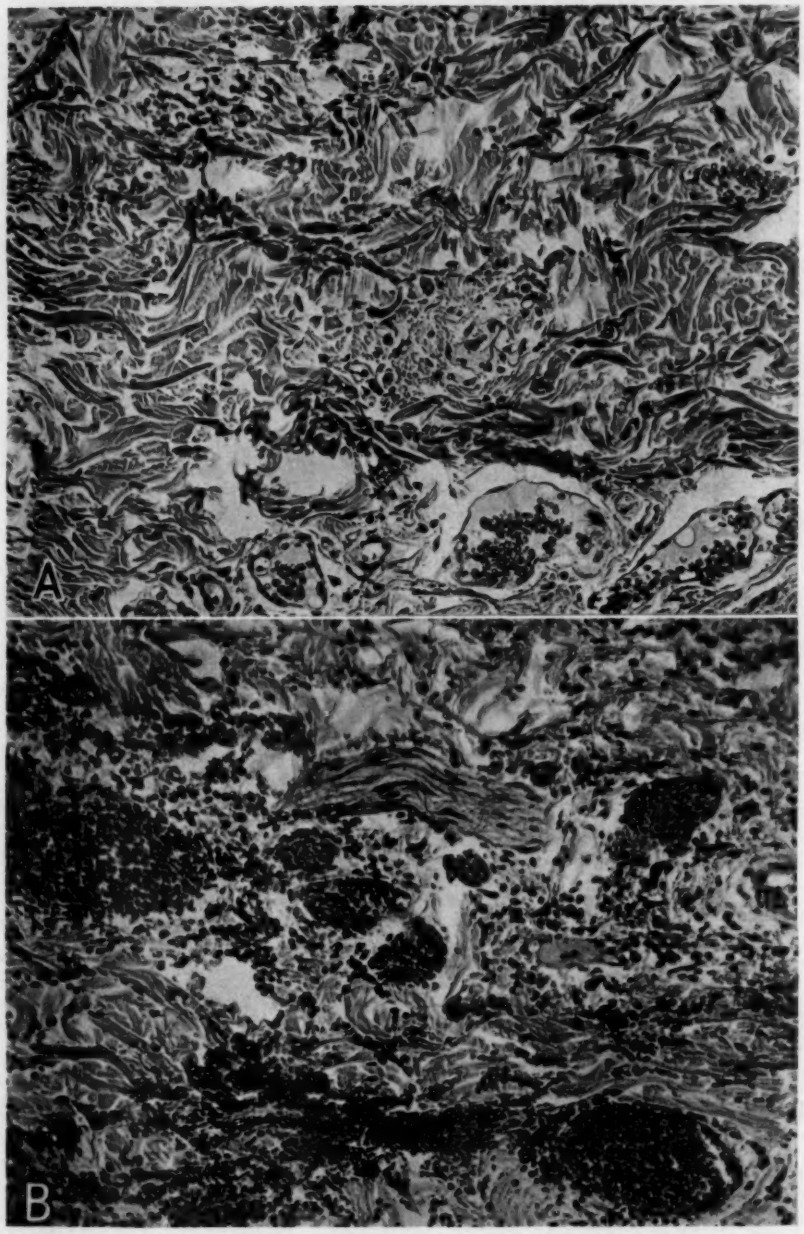

Fig. 4 (group C, subgroup 3).—*A* shows a section of the skin site after preparation with typhoid bacillus filtrate almost completely neutralized by homologous antitoxic horse serum, followed twenty-four hours later by the intravenous injection of 25 reacting units of the same filtrate. Four hours after intravenous injection there were only slight inflammation and moderate vascular congestion. *B* shows a section of the skin site after preparation with nonneutralized typhoid bacillus filtrate, followed twenty-four hours later by intravenous injection of 25 reacting units of the same filtrate. The skin four hours later presented the typical phenomenon, with marked hemorrhage and inflammatory reaction.

It is clearly demonstrated by the results in this experiment that although identical degrees of inflammation following skin preparation occurred with both the partially neutralized and the nonneutralized filtrate, the inflammatory reaction seen with the phenomenon was in direct proportion to the extent of the ability of the filtrate to prepare the skin for the phenomenon but not to the degree of inflammation produced on intradermal injection.

Group D: Skin Preparation with a Nonphenomenon-Producing Substance.—A comparison was made of the effect of a nonphenomenon-producing substance when injected intradermally alone and the result when a subsequent injection of intravenous factors usually capable of eliciting the phenomenon was given. A rabbit received 0.25 cc. of a 1:50 dilution of silver nitrate solution intradermally. The skin site was removed twenty-eight hours later. Grossly there was a slightly elevated, sharply circumscribed, pale gray central area of necrosis, 0.5 cm. in diameter, surrounded by a pink wheal that faded gradually into the surrounding skin. Microscopically there was a massive collection of leukocytes extending from the epithelium through the subcutaneous tissue. The cells showed marked degenerative changes, particularly in the central portion of the mass, where small foci of necrosis were present. At the edges the infiltrated area was marked off by a zone of edema, discrete leukocytic infiltration and capillary congestion. No hemorrhages were present. The overlying epithelium was infiltrated by leukocytes, and the cells were swollen; many cells were degenerated.

A second rabbit received a similar intradermal injection, followed twenty-four hours later by the injection of 25 reacting units of typhoid bacillus filtrate intravenously. The skin site was removed four hours after intravenous injection. Both grossly and microscopically, the changes in this instance were identical with those when no intravenous injection was given.

It is evident, therefore, that silver nitrate is incapable of preparing the skin for the elicitation of the Shwartzman phenomenon in the rabbit. The inflammation produced by the intradermal injection of the silver nitrate solution was in no way enhanced by the subsequent intravenous injection of bacterial filtrate.

Group E: Elicitation of the Phenomenon with a Bacterial Filtrate of Low Potency.—Four rabbits received an intradermal injection of 0.5 cc. of an undiluted filtrate of Streptococcus haemolyticus. Twenty-four hours later three of the animals received 25 reacting units of a meningococcus filtrate intravenously. The skin was removed four hours after intravenous injection. Similarly, the skin of the animal that did not receive an intravenous injection was removed at the same time. Grossly, the skin of the latter animal showed an irregular, slightly raised pinkish area at the site of injection. Histologically, a moderately severe degree of inflammation was evident, not very different from that described in the protocols for animals used in the studies of group A. Capillary congestion was present to a moderate extent.

The skin of the three animals that received both the intradermal and the intravenous injection showed grossly erythematous areas about 1.2 cm. in diameter, somewhat elevated above the surface. One of these areas presented, in addition to the erythema, a darker center, somewhat raised above the swollen skin, with tiny irregular purpuric spots. Histologically, the changes presented in all three sections were similar. There were moderately marked dilatation and congestion of the capillaries with small foci of hemorrhage into the corium and subcutaneous tissues, moderate leukocytic infiltration with characteristic arrangement about the blood vessels and occasional thrombosis of the small veins. The thrombi were usually parietal and had the appearance of those observed in the studies of

group B. They were surrounded by masses of red cells in dilated vessels. No significant alteration of the walls of the vessels was seen. Only occasional foci of necrosis were evident. The histologic picture was that of a mild hemorrhagic and inflammatory reaction.

Group F: Skin Preparation Followed by a Second Intradermal Injection of Bacterial Filtrate into the Same Site.—For the purpose of comparing the changes in the skin produced by repeated intradermal injections with those observed in the typical phenomenon, a rabbit was given intradermally 0.25 cc. of typhoid bacillus filtrate, equivalent to 187 reacting units. Twenty-four hours later a similar dose was injected into the same site, and the skin was removed four hours later. Grossly, there was an area of edema 2.5 cm. in diameter, of deep red. No gross hemorrhages were seen. Microscopic examination revealed a severe degree of inflammation, characterized by marked edema and extensive infiltration with polymorphonuclear leukocytes. There was marked perivascular infiltration, and at times the cells infiltrated the entire wall of the vessel. However, no thromboses were present. Hemorrhage was likewise absent. Many of the capillaries were dilated and engorged. Small foci of necrosis were scattered in the subcutaneous tissues.

Although the severity of the inflammation can be readily compared with that seen in the phenomenon, the absence of thrombosis and hemorrhage readily serves to distinguish the picture produced in this test from that observed in the typical phenomenon. It must be mentioned that the amount of filtrate employed for repeated intradermal injections was many times greater than that used to obtain the phenomenon. This will be discussed subsequently.

THE ARTHUS PHENOMENON

The changes in the skin attendant on the production of the Arthus phenomenon were studied for comparison with those seen in the Shwartzman phenomenon.

Six rabbits were used. Two received a single intradermal injection of 0.5 cc. of normal horse serum, and the skin site was removed one and three days later, respectively. The remaining four animals each received a second intradermal injection of a similar amount of horse serum, one week after the first, and one of these rabbits was killed four hours after the second injection. Two weeks after the first injection the remaining three animals received a third intradermal injection, and one of these was killed four hours later. Similarly, three and four weeks after the first injection the fifth and sixth animals, received, respectively, a fourth and a fifth intradermal injection, and each was killed four hours after the final injection. The series thus included animals killed at the following intervals: one day and three days after a single intradermal injection and at the end of one week, two weeks, three weeks and four weeks, during which period the animals received, respectively, two, three, four and five intradermal injections of normal horse serum.

Grossly, at the site of a single injection there were only slight erythema and swelling, which disappeared within a day. There were correspondingly increasing degrees of redness and swelling with each subsequent injection. The reaction was much greater than that seen with skin preparation by bacterial filtrates. The areas measured, as a rule, about 2.5 by 1.5 cm., and the fourth and sixth animals showed punctate hemorrhages in the edematous skin site after the final injection. In each instance, the swelling and erythema persisted for a longer period after the intradermal injection as the number of injections was increased.

The histologic features were essentially identical with those described by Gerlach.[8] A single injection of horse serum produced only slight edema with discrete leukocytic infiltration. This reaction subsided within three days. After repeated injections striking edema was noted, with swelling of the collagen and a central acellular area surrounded by a zone of leukocytic infiltration and capillary congestion. The collagen fibers lost their fibrillar structure. The blood vessels were surrounded by collars of leukocytes, which often infiltrated the walls. The walls of many of the small arteries were hyalinized. In some instances the vessels were necrotic and filled with large thrombi. In one instance a parietal thrombus in a large vein was organized. Within the acellular central area the capillaries were collapsed, and only occasional leukocytes were present. In addition to the leukocytes, many of which showed decided degenerative changes, there were many macrophages, lymphocytes and plasma cells. Focal areas of necrosis and scattered hemorrhages were likewise present. The muscle fibers appeared waxy and swollen. In the vicinity of the necrotic foci the vessels often showed degenerative changes of the endothelium.

Gerlach described hemorrhages in the later stages of the Arthus phenomenon, but not as an outstanding feature. The central acellular areas of collagen swelling and necrosis characteristic of the Arthus phenomenon are not observed in the Shwartzman phenomenon.

COMMENT

The degree of inflammation that may follow skin preparation depends to a great extent on the amount of bacterial filtrate injected. Also, filtrates of various micro-organisms produce different degrees of inflammation. Likewise, filtrates of organisms that possess little skin-preparatory potency, such as Str. haemolyticus, occasion moderate or marked inflammation with skin preparation. Nevertheless, there is no parallelism between the skin-preparatory potency of a filtrate and the inflammation resulting from its intradermal injection. This is demonstrated in the results obtained in the experiments of subgroups 3 of group C, in which identical degrees of inflammation resulted from skin preparation with filtrate almost completely neutralized by homologous antitoxic horse serum and from skin preparation with nonneutralized filtrate. The former filtrate, however, is capable of only partially preparing the skin, so that after intravenous injection of the reacting factors only a 1 plus phenomenon is obtained. Similarly, a filtrate may possess a high degree of skin-preparatory potency and yet the inflammation seen after intradermal introduction may be slight, as observed in the experiment in subgroups 1 of group C. In this instance the elicitation of the phenomenon resulted in as severe a reaction as that seen with the use of filtrates that produced much greater degrees of inflammation with skin preparation.

Although Apitz described inflammation associated with skin preparation, he did not consider it of significance in the subsequent appearance of the phenomenon. Karsner and Moritz expressed the belief that the

8. Gerlach, W.: Virchows Arch. f. path. Anat. **247**:294, 1923.

inflammation occurring with skin preparation must be present in order to create a state of reactivity of the tissues. Freund [9] suggested that the intensity of the hemorrhagic and inflammatory response seen in the phenomenon was dependent on the degree of inflammation occurring with skin preparation. However, the determining factor in the production of the phenomenon is not the inflammation attendant on skin preparation but rather the actual preparedness of the skin. The degree of inflammation occurring with skin preparation is no index of the state of preparedness of the skin. For example, in subgroup 2 of group C it was pointed out that forty-eight hours after skin preparation the inflammation was still severe, yet the state of preparation of the skin was so lowered that it required four times the usual quantity of filtrate to elicit the phenomenon. Similarly, the degree of inflammation produced with skin preparation does not determine the extent of the inflammatory reaction seen on production of the phenomenon. This is well demonstrated in the experiments of subgroups 1 and 3 of group C, in which the inflammation produced by elicitation of the phenomenon is dependent not on that caused by skin preparation but on the extent of preparedness of the skin.

This lack of parallelism between the extent of inflammation accompanying skin preparation and that associated with the phenomenon was also noted by Apitz and Kielanowski and Selzer. Karsner and Moritz described severe inflammatory changes following local preparation for the phenomenon and attributed it to the fact that their filtrates were concentrated. They concluded that the preparatory factors were irritant and that the effects varied with the degree of concentration and with the reactivity of the animal. Undoubtedly, artificially concentrated filtrates containing such substances as acetic acid exhibit greater irritating effects and, if injected intravenously, kill the animal. Even unconcentrated filtrates possess primary toxicity. But whether the toxicity is bound up with the preparatory or with the reacting factors is still undecided. However, there is evidence to support the belief that the factors in the filtrate capable of producing skin preparation are distinct from those responsible for inflammation. The results in the experiments of subgroup 3 of group C indicate that it is possible tc neutralize the skin-preparatory factors. The substances responsible for the inflammatory reaction, however, remain unchanged, as evidenced by the similar degree of inflammation produced by the injection of nonneutralized filtrate as a control.

It is still not known what substances in the filtrate are responsible for the inflammation. As seen in the control studies, the fluid medium in which the filtrate is suspended (phenolized saline solution) and the

9. Freund, J.: J. Exper. Med. **60**:661, 1934.

possible particles of the solid medium on which the organism is cultured (plain or dextrose agar) are in themselves capable of producing a certain degree of inflammation. Perhaps autolyzed organisms, unavoidably present in the filtrate, contribute to the inflammation. Since intradermal injections of a filtrate of high skin-preparatory potency result in minimal inflammation no greater than that of the controls, it would appear that the preparatory factors are in themselves not responsible for the inflammation.

The results of Hanger's [10] experiments with bacterial allergy would suggest that in some instances this factor might account for the inflammatory reaction incident to skin preparation. However, since the inflammation is seen after intradermal injection of filtrates of organisms which normally do not exist in the host (rabbit), such as the meningococcus, and since it occurs in 100 per cent of the animals tested, it is not likely that bacterial allergy alone accounts for this inflammation. However, when filtrates of organisms that exist in the host are employed, bacterial allergy may be an additional factor in the occurrence of inflammation with skin preparation. The degree of inflammation varied considerably in individual instances in the series of animals observed in this study. Shwartzman, in his first reports on the phenomenon, called attention to this individual variation.

The earliest changes that follow the injection of the reacting factors for the production of the phenomenon are extensive capillary and venous dilatation and congestion, hemorrhage and vascular thrombosis. Concurrently, there is accentuation of the preexisting inflammation, so that even when moderately severe inflammation occurs with skin preparation the increase which follows the phenomenon can be readily discerned. Hemorrhage precedes the thrombosis. Subsequently, there is an increase in the degree of both, so that when the reaction has reached its peak these alterations dominate the picture.

Although Kielanowski and Selzer, and Karsner and Moritz described the regular occurrence of hemorrhage and thrombosis with skin (or other local) preparation alone, these reactions were not observed in the present study. Thus, Karsner and Moritz considered that the phenomenon differs from the skin preparation or local preparation only quantitatively. Certainly, that would seem to be true when concentrated or broth filtrates are employed for skin preparation. In these instances it is difficult to determine the part that nonspecific substances present contribute to the changes. In the present study, in which filtrates of high skin-preparatory potency were used so that only small quantities were necessary and the amount of nonspecific, irritating substances was greatly reduced, the absence of hemorrhage and thrombosis with skin

10. Hanger, F. M.: Proc. Soc. Exper. Biol. & Med. **25**:230 and 775, 1928.

preparation was a constant feature. Thus, the appearance of hemorrhage and thrombosis with accentuation of the inflammation served to differentiate the phenomenon from skin preparation qualitatively as well as quantitatively.

The cause of the hemorrhages could not be ascertained morphologically. Although occasional ruptured capillaries were seen in sections of skin showing the phenomenon, it was not possible to attribute the extensive hemorrhage to these alterations. Kielanowski and Selzer, on the other hand, described the frequent occurrence of ruptured capillaries, and they expressed the belief that this condition resulted from sudden overfilling with blood. Apitz observed only scattered ruptured vessels. As the endothelial changes were slight, he considered that the hemorrhages resulted from diapedesis.

The most striking morphologic change occurring in the skin with the appearance of the phenomenon, in addition to hemorrhage, was the presence of widespread thrombosis, affecting chiefly the veins. The thrombi consisted of amorphous masses that stained deeply pink with eosin, mixed with scattered leukocytes and erythrocytes. With the Weigert stain little fibrin was noted, chiefly about the periphery of the thrombus. At the site of attachment of the thrombus endothelial alterations were not noted. The affected vessels were surrounded by thick collars of polymorphonuclear leukocytes; these often infiltrated the entire wall of the vessel. Changes in the elastica were absent.

There are a number of factors that could account for the thrombosis. Chief among these are the slowing of the circulation, evidenced by widespread vascular dilatation and engorgement, and extensive perivascular inflammation. These factors alone, however, are insufficient to give rise to such extensive thrombosis formation, as Dietrich [11] has shown. Nevertheless, morphologic proof of endothelial damage was lacking in the main, both in these studies and in those reported by Kielanowski and Selzer, and Apitz.

The concept of endothelial hyperactivity advanced by Dietrich and the presence of other factors may serve to explain the origin of the thrombi. Endothelial hyperactivity may be initiated in this instance by the skin-preparatory injection. When this is followed by a second stimulus which reaches the vessel by way of the blood stream (reacting factors) and when there are simultaneous slowing of the circulation and perivascular inflammation, thrombosis results. Further studies on the subject are necessary, particularly on the endothelial response to preparatory factors, before a satisfactory conclusion can be reached.

11. Dietrich, A.: Thrombose, ihre Grundlagen und ihre Bedeutung, Berlin, Julius Springer, 1932.

Organization of the thrombi is initiated by proliferation of the endothelium, which rapidly grows over the surface of the thrombotic masses. Subsequently, there are invasion of the thrombus by fibroblasts from the walls of the vessels and complete organization.

The extent of thrombosis is not quantitatively dependent on the degree of inflammation present with skin preparation or on that occurring with the phenomenon. During the first twenty-four hours there may be increase in the degree of thrombosis, possibly as a result of extension of the concurrent inflammation. The degree of thrombosis varies with the type of the reacting factor as well as with the skin-preparatory qualities of the filtrates employed. For example, experiments on the elicitation of the phenomenon by the use of the antigen-antibody combination as the reacting factor (Shwartzman [12]) demonstrated a more marked degree of thrombosis than when filtrates of typhoid bacilli are injected intravenously, even though in both instances the skin preparation was productive of identical degrees of moderate inflammatory reaction.

The necrosis of tissue succeeding the full development of the phenomenon can be ascribed both to the primary effect of the toxic filtrates on the local tissues and to the resultant disturbance in circulation following hemorrhage and thrombosis.

Shwartzman, in earlier studies on the phenomenon, pointed out that repeated injections of bacterial filtrate at the same skin site would not produce the typical phenomenon. Apitz, in a similar investigation, emphasized the inflammatory response characterized by edema and leukocytic infiltration following the second intradermal injection and interpreted the reaction as local anaphylactic inflammation. A review of the observations in group F indicates that Shwartzman's observations can also be confirmed morphologically. Despite the fact that the rabbit received a total of 374 reacting units of typhoid bacillus filtrate intradermally, the essential characteristics of the typical phenomenon, namely, hemorrhage and thrombosis, were not produced. The amount of filtrate used represents almost fifteen times the quantity necessary to elicit the phenomenon in the usual manner. The inflammation following repeated intradermal injections was not more striking than that seen in the typical phenomenon, such as that elicited in the experiments of group B. No doubt, the arrival of the second dose at the local site directly through the vessels is of special significance in the production of hemorrhage and thrombosis. Shwartzman [13] suggested that the reacting factors are modified in vivo after intravenous injection, so that the resultant reaction

12. Shwartzman, G.: Science **76**:127, 1932.

13. Shwartzman, G.: J. Exper. Med. **56**:687, 1932.

is qualitatively different from that seen after repeated intradermal injections.

Freund suggested that the Shwartzman phenomenon represents an augmentation of inflammation subsequent to skin preparation by the intravenously injected filtrate. Menkin [14] expressed the belief that the chief mechanism underlying the phenomenon is the fixation of the intravenously administered dose of filtrate at the site of the inflammation produced by skin preparation. The basis for this concept lies in the demonstration by Opie,[15] Menkin and others that intravenously administered substances, such as bacteria, dyes and proteins, tend to become localized or attracted to a site of nonspecific inflammation. No doubt, the inflammation following skin preparation may, in the manner of any nonspecific inflammation, attract to the local site the intravenously administered filtrate. Yet this does not explain the entire phenomenon. As has been shown in the experiments with silver nitrate, the inflammation is in no way altered after the intravenous injection of bacterial filtrate, since silver nitrate cannot prepare the skin of the rabbit for the phenomenon. Shwartzman has demonstrated this amply with a large group of nonspecific substances. The studies with the use of neutralized and nonneutralized bacterial filtrates conclusively demonstrate that the inflammation produced with skin preparation is readily distinguishable from the preparedness of the skin for the phenomenon and hence that it plays no significant rôle in the production of the phenomenon. The essential factors in the production of the phenomenon are the state of preparedness of the skin, which is independent of the associated inflammation, and the action of the intravenously administered reacting factors. The latter, altered in vivo, act on the prepared site and lead to a greatly heightened response of the local tissues.

The Shwartzman phenomenon has been frequently considered as a variant of the Arthus phenomenon, because of certain morphologic similarities between them. On morphologic grounds alone it is not entirely possible to distinguish the two phenomena, especially since it has been demonstrated by Apitz that with certain modifications of the Arthus phenomenon histologic pictures identical with those observed in the Shwartzman phenomenon could be obtained. Shwartzman pointed out the distinct immunologic differences between the phenomenon of local reactivity to bacterial filtrates and that of Arthus. Obviously, the identification on purely morphologic grounds of two phenomena apparently unrelated immunologically is not warranted. Furthermore, there are certain histologic features in the evolution of the two phenomena which lend morphologic support to their immunologic differen-

14. Menkin, V.: Arch. Path. **12**:802, 1931.
15. Opie, E. L.: J. Immunol. **17**:329, 1929.

tiation. The earliest changes seen in the Shwartzman phenomenon are extreme vascular dilatation and engorgement, hemorrhage and thrombosis with concurrent severe inflammation. In the Arthus phenomenon three injections of normal horse serum, given a week apart, are productive only of increasingly severe edema and inflammation. Vascular damage occurs only later in the course of the phenomenon, usually in the fourth week. The Arthus phenomenon is attended also by a much less marked degree of hemorrhage, isolated vascular thrombosis and nonhemorrhagic necrosis of the collagen.

SUMMARY AND CONCLUSIONS

Histologic studies of the Shwartzman phenomenon confirm the reports of previous observers of the occurrence of inflammation subsequent to skin preparation. However, it can be clearly established that the inflammation is nonspecific and bears no relation to the preparedness of the skin for the phenomenon. These observations lend morphologic support to Shwartzman's [2] concept that the preparatory factors induce a state of vulnerability of the tissues which is "not in the nature of a mere trauma, increased permeability of capillaries or inflammation, but which is probably due to some functional disturbance in the cells which requires a short incubation period for its appearance and which disappears rapidly."

The phenomenon is not an expression of augmentation of the inflammation present with skin preparation, since the changes in the tissues occurring in the elicitation of the phenomenon are not dependent on the preexisting inflammation but rather on the actual preparedness of the skin. While the fixation of intravenously administered substances at the site of a local inflammation may play a rôle in the appearance of the phenomenon, this is only an incidental factor. Chemicals or neutralized filtrates cannot prepare the skin for the phenomenon, and the local inflammation produced by them is unaffected by intravenous injection of reacting factors.

There is no basis for considering the inflammation seen with skin preparation in the Shwartzman phenomenon as allergic. Although certain morphologic similarities exist between the phenomenon of Arthus and that of Shwartzman, they can be accurately differentiated immunologically and, to a certain degree, morphologically.

Case Reports

GELATINOUS CARCINOMA OF THE PANCREAS

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Cylindric cell carcinoma of the pancreas occasionally undergoes extensive gelatinous changes. Ewing,[1] Aschoff[2] and Kaufmann[3] mentioned this retrogressive alteration briefly. Wilks[4] described a gelatinous tumor involving almost the entire pancreas. A small region in the head of this organ was free from the tumor, and metastatic nodules were present only in the omentum. This lesion occurred in a 56 year old man in whom diffuse abdominal pain, constipation and rapid loss in weight were the only symptoms noted during the last six months of life.

A similar clinical picture in a 44 year old man was reported by Mosler.[5] At autopsy the pancreas was completely transformed into a large nodular mucoid tumor mass. Numerous small secondary growths were found in the regional lymph nodes, the omentum and the liver. The latter record is the basis for Weyer's inaugural dissertation.[6]

Lücke and Klebs[7] described an enormous fluctuant tumor in the abdominal cavity of a 43 year old woman. The clinical diagnosis was ovarian cyst. At operation a large saclike structure filling the greater part of the peritoneal cavity was opened and found to contain considerable milky fluid. This mass was not attached to either ovary. Three days later death occurred from postoperative shock. At the postmortem examination it was found that papillary gelatinous excrescences formed the floor of the cystic structure. These were continuous with large mucoid nodules in the pancreas. There were small gelatinous nodules in the mesenteric lymph nodes and the serosa of the transverse colon and larger masses in Douglas' culdesac and the left broad ligament. The authors concluded that this tumor had its origin in the

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1. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1931, p. 747.

2. Aschoff, L.: Pathologische Anatomie, ed. 6, Jena, Gustav Fischer, 1923, vol. 2, p. 904.

3. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, ed. 9 and 10, Berlin, G. Reimer, 1931, vol. 1, p. 987.

4. Wilks: Tr. Path. Soc. London **6**:224, 1854.

5. Mosler, F.: Deutsches Arch. f. klin. Med. **28**:493, 1880-1881.

6. Weyer, G.: Ein Fall von Gallertkrebs des Pankreas, Inaug. Dissert., Greifswald, C. Sell, 1881.

7. Lücke, A., and Klebs, E.: Virchows Arch. f. path. Anat. **41**:1, 1867.

pancreas. It had extended into the omental bursa and formed a large cystlike mass.

Gilmer,[8] Ward,[9] Rheiner,[10] Helly [11] and Kaufmann [3] each reported an instance of mucoid carcinoma limited to the tail of the pancreas. There was no clinical indication of pancreatic disease in any of these. In one instance, small gelatinous nodules studded the peritoneum; in another, secondary growths were seen in the retroperitoneal nodes near the pancreas, in the periaortic nodes and in the liver and lungs. In a third, the peritoneum, omentum, liver, spleen, kidneys and lungs contained numerous tumor nodules. Another record [8] describes a large gelatinous tumor in the tail and body of the pancreas. Metastatic nodules were limited to the liver.

Multiple large gelatinous nodules in the lungs of a 52 year old woman are described by Osler.[12] These were associated with a small scirrhous carcinoma in the body of the pancreas. Inasmuch as no microscopic examination was made of the neoplasm in the pancreas, one may conclude that small areas of gelatinous carcinoma were overlooked.

Gelatinous carcinoma confined to the head of the pancreas has been observed by Kaufmann.[3] Rheiner [10] reported a similar neoplasm with occlusion of the duct of Wirsung. Compression of the ductus choledochus and portal vein by this tumor has caused jaundice and ascites. Metastases were found in the liver and hepatoduodenal ligament. In a second case, Rheiner observed mucoid carcinoma constricting the pancreatic and common bile ducts near the ampulla of Vater. An ascending cholangeitis contributed to the severe jaundice.

Carcinoma originating in the head of the pancreas is often grossly indistinguishable from carcinoma arising in the second portion of the duodenum or in the papilla of Vater. An accurate microscopic study is essential, and even then it is at times impossible to determine the origin of the neoplasm.

It has been suggested that a malignant tumor invading the head of the pancreas and duodenum has its genesis [13] in aberrant pancreatic tissue. However, even though islands of pancreatic tissue are common in the wall of the duodenum and about the pancreas it has never been proved that these give rise to carcinoma.

The first thorough histopathologic study to determine the origin of mucoid carcinomas of the pancreas was made by Rheiner.[10] Prior to his investigation, epithelial and goblet cells of the ducts were believed to be the only cells of origin.[14] Rheiner, however, concluded from his

8. Gilmer, Ludwig: Ueber das primäre Carcinom des Pancreas im Anschluss an zwei Fälle von primären Schleimkrebs der Cauda pancreatis, Inaug. Dissert., Freiburg i. Br., M. Hochreuter, 1899.

9. Ward, S. B.: Albany M. Ann. **20**:24, 1899.

10. Rheiner, P.: Ein Beitrag zur Pathologie der Pankreasschleimdrüsenkarzinome, Inaug. Dissert., Zürich, Weida i. Thür., Thomas & Hubert, 1925.

11. Helly, K.: Virchows Arch. f. path. Anat. **261**:68, 1926.

12. Osler, William: M. News **42**:694, 1883.

13. von Heinrich, Hans: Virchows Arch. f. path. Anat. **198**:392, 1909.

14. Ssobolew, L. W.: Beitr. z. path. Anat. u. z. allg. Path. **47**:399, 1910.

study that many gelatinous carcinomas of the pancreas are derived from mucous glands. These glands are normal appendages of the pancreatic duct and its larger branches. He described hyperplasia with papillary formation of the mucous glands in pancreatic tissue adjacent to a carcinoma. This hyperplasia became more atypical as the neoplasm was approached. He demonstrated a direct and gradual transition from mucus-producing glands into gelatinous carcinoma. He called these tumors mucous gland carcinomas (*Schleimdrüsenkarzinom*). Their origin was similar to the bronchiogenic and bile duct carcinomas arising from mucous glands.

Helly [11] concurred in the opinion that gelatinous carcinomas of the pancreas frequently originate from mucous glands. He observed seven instances of mucoid carcinoma but failed to state the localization and structure in six. In the seventh, the histologic presentation of a carcinoma in the tail of the pancreas is almost identical with the picture depicted by Rheiner. There is no adequate explanation offered for this high incidence of gelatinous carcinoma, which is contrary to observations made by other investigators.

CASE 1

A white woman, aged 58, was admitted to the Los Angeles County Hospital on Feb. 27, 1935, complaining of chills, fever and weakness. These symptoms were of two months' duration. A yellow discoloration of the skin had been present during the last two weeks. Hematemesis and tarry stools were noted for the first time one day prior to her admission to the hospital.

The patient was jaundiced and appeared acutely ill. There was slight rigidity of the abdomen; no masses could be palpated.

The icterus index was 57; the van den Bergh reaction was immediate and direct. Hemoglobin was 35 per cent, with 2,500,000 red cells in each cubic millimeter.

The patient died one day after admission. The clinical impression was that a hemorrhage had occurred secondarily to carcinoma of the stomach or of the ampulla of Vater.

Autopsy (Louisa Hemken) twenty hours after death revealed a fairly well nourished white woman. The scleras and skin were yellow; the lips and gums, very pale.

The peritoneal cavity contained 30 cc. of bloody fluid. The visceral peritoneum was purple-red, smooth and glistening. In the head of the pancreas was a mucoid nodular tumor mass. This extended through the wall of the duodenum. It formed a gelatinous excrescence 5 by 3 cm. in diameter in the mucosa of the second portion of the duodenum. This projection was partially covered with loosely adherent soft blood clots; an edematous patent papilla of Vater was distinguishable near one edge.

The body and tail of the pancreas were hard, but there were no tumor masses.

The stomach contained 6 ounces (177.4 cc.) of blood-tinged fluid. The duodenum, jejunum, ileum and large intestines were distended with large blood clots. The mucosa, except the region in the duodenum occupied by tumor, was normal but pale.

The liver weighed 1,750 Gm. It was soft and greenish yellow. Several small circumscribed yellow nodules were present in the right lobe. The gallbladder was considerably distended, its wall thin and the lumen filled with thick blood-

stained purulent fluid. The cystic and common bile ducts were dilated and filled with similar material. The lining of the ducts was normal.

The spleen weighed 150 Gm. It was pale red and the pulp extremely soft.

There was a terminal bronchopneumonia. No significant pathologic alterations were present in the other organs.

Microscopic Examination.—The nodular tumor mass in the pancreas consisted of spaces filled with a pale blue substance (hematoxylin and eosin stain) and numbers of cells. These spaces were of variable dimensions and were separated from each other by narrow bands of cellular stroma. The small spaces were lined with uniform columnar epithelial cells. The larger irregular spaces were bounded by atypical epithelium. The oval hyperchromatic nuclei were located basally in the cells; a few mitoses were found. Swollen epithelial cells, leukocytes and red blood cells were present in the mucus-filled spaces.

Interstitial and intralobular pancreatitis was noted in the remnants of pancreatic tissue still present in the deepest portion of the head of the pancreas, that is to say, the part farthest removed from the duodenum. Collections of lymphocytes, plasma cells and eosinophils were lodged between the connective tissue fibers. In some places, however, there were accumulations of polymorphonuclear leukocytes and areas of recent hemorrhage. The epithelium in the small and medium-sized branches of the pancreatic duct was hyperplastic, and an occasional nodule of mucoid carcinoma was present. As the duodenum was approached, there was a diminution in the acinar tissue with a transition from hyperplasia of the ducts into mucoid carcinoma. Islands of carcinoma separated the muscle fibers in the duodenal wall. Other islands, definitely separated from the duodenum, formed an apron-like covering over the villi.

The material in the tumor spaces was identified as mucin by the mucicarmine stain.

In the liver there was hyperplasia of the small bile ducts; these were surrounded by dense aggregates of polymorphonuclear leukocytes, mononuclears and lymphocytes. Numbers of small abscesses were present in the portal triads. There were parenchymatous degeneration and deposition of biliary pigment in the hepatic lobules.

Comment.—The gross observations at necropsy failed to disclose a definite origin of the mucoid carcinoma. The fact that the tumor occupied practically the entire head of the pancreas suggested a pancreatic origin. The histopathologic study, however, indicated a genesis from epithelial or goblet cells of the pancreatic duct. In the deepest portions of the head of the pancreas not involved by tumor, there was hyperplasia of the ducts and, as the tumor was approached, transition into carcinoma. Furthermore, the tumor cells overlay and appeared definitely demarcated from the duodenal mucosa. There was also chronic pancreatitis, which is a frequent forerunner of malignant growth in the pancreas.

A superimposed acute pancreatitis was responsible for the ascending suppurative cholangeitis. The extension of the carcinoma into the duodenum, associated with a brisk hemorrhage, hastened the demise of this patient.

CASE 2

An American laborer, aged 65 years, entered the Los Angeles County Hospital on Feb. 26, 1935, with a history of vague pain in the upper abdominal region

and constipation of two months' duration. Weakness and shortness of breath had been noticed for four weeks.

A firm irregular mass was palpable in the epigastrium. The blood pressure was 169 mm. of mercury systolic and 130 mm. diastolic. The temperature was 98 F.; the pulse rate, 80 per minute, and the respirations, 20.

The histamine test for gastric function revealed a maximum of 3 degrees of free acid. The Wassermann reaction of the blood was negative.

The patient went into a state of shock and died suddenly nine days after his admission to the hospital.

Autopsy (H. A. Edmondson) twenty-three hours after death revealed a fairly well nourished white man.

The peritoneum was smooth and glistening. The head of the pancreas was occupied by a large gelatinous tumor extending posteriorly and forming a bulky mass in the retroperitoneal tissues. The pancreatic duct was readily found in the head of the pancreas. Immediately adjacent to the duct, just a short distance from the point at which it entered the duodenum, was a cyst, 4 cm. in diameter, filled with hemorrhagic mucoid fluid. From the wall of this cyst small papillary gelatinous nodules projected into its lumen. The inferior vena cava and abdominal aorta were compressed by large lymph glands filled with gelatinous nodules.

Both pleural cavities were obliterated by dense fibrous adhesions. In the lobes of the lungs were many diffusely distributed gelatinous nodules, 1 to 12 mm. in diameter. There was marked pulmonary edema, and many small branches of the pulmonary artery were occluded by antemortem thrombi.

Changes in the other organs were consonant with the age of the patient and insignificant so far as this report is concerned.

Microscopic Examination.—The cyst in the head of the pancreas was lined with a single layer of columnar epithelium. Its wall was composed of hyaline connective tissue and numbers of lymphocytes. In one region a few daughter cysts were present, the larger one filled with mucus and communicating with the main cyst. Immediately adjacent to this daughter cyst was a mucoid carcinoma similar in structure to the carcinoma described in the first case. Between the acini of the tumor was a densely cellular and vascular stroma with a few small islands of atrophic pancreatic lobules and small pancreatic ducts. In another section from the head of the pancreas, some distance from the cyst, there was considerable chronic interstitial pancreatitis in the area not involved by tumor. There was hyperplasia of the small branches of the pancreatic ducts; many were distended with mucus.

The metastatic nodules in the lungs, lymph nodes and retroperitoneal tissues presented the same microscopic appearance as the primary neoplasm in the head of the pancreas.

The substance within the tumor spaces gave the characteristic reaction for mucin.

Comment.—The presence of a cyst in close proximity to the carcinoma in case 2 naturally suggested a genesis from the wall of the cyst. The localized area in the wall of the newly formed cyst showing irregular smaller cysts supported this theory. Even though the histologic study favored this origin, the evidence was not entirely conclusive. It could not be definitely determined whether the cyst had resulted from obstruction to the pancreatic duct by tumor or whether it was independent of the carcinoma.

Scola [15] described two large pancreatic cysts, one combined with carcinoma and the other with sarcoma. In both he was able to demonstrate malignant changes in the cyst wall. Hopkins [16] described early carcinomatous changes in the wall of a large cyst located in the head of the pancreas. Nevertheless, it is well known that retention cysts of the pancreas are only occasionally associated with malignant growth.

SUMMARY

An origin from mucous glands normally present along the pancreatic duct is demonstrable in a few of these carcinomas. The majority, however, arise from epithelial or goblet cells lining the pancreatic duct. Retention cysts in the pancreas are seldom associated with malignant growth.

Clinical recognition is difficult. Quantitative determinations of neutral fat and fatty acids in the feces should be made whenever carcinoma of the pancreas, the ampulla of Vater or the second portion of the duodenum is suspected. These fats are frequently increased far above the normal with carcinoma of the pancreas.

Gelatinous cylindric cell carcinoma of the pancreas is uncommon. I have cited the records appearing in the literature and now add two cases of mucoid carcinoma in the head of the pancreas.

15. Scola, A.: Ueber krebsige und sarkomatöse Entartung von Pankreascysten, Inaug. Dissert., Greifswald, H. Adler, 1902.

16. Hopkins, J. G.: Proc. New York Path. Soc. **12**:135, 1912.

General Review

THE SPECIFIC IMMUNITY RESPONSE AND THE HEALING OF INFECTIOUS DISEASES

SIGNIFICANCE OF ACTIVE IMMUNITY AND THE CONNECTIONS BETWEEN THE IMMUNITY RESPONSE AND THE ANATOMIC LESIONS

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The most important advance in the study of infectious diseases since the recognition of their parasitic nature has been the discovery of the specific antigenic response. By this discovery the way for the understanding of healing and immunity was opened. Beginning with the use of diphtheria antitoxin, the concept of the humoral antibodies was applied to the diagnosis and treatment of infectious diseases with such brilliant results that there has been an almost irresistible tendency to assume that all the specific phenomena of healing and immunity may be explained by the effect of humoral antibodies.

Such an assumption in many instances finds sufficient experimental support. The immunity of the tissues against diphtheria toxin as well as the immunity of the whole organism, for instance, runs closely parallel to the concentration of antitoxin in the blood stream. The explanation of the mechanism of anaphylaxis was an impressive theoretical success of serology. Yet almost from the beginning of immunologic investigation it was apparent that certain classes of specific phenomena are not in connection with circulating antibodies and cannot be reproduced by passive immunization. A part of these phenomena can be explained by assuming that antibodies are produced locally but that for some accidental reason they do not appear in the circulation. The local immunity of the eye to abrin, which Römer observed before the development of general immunity, and the healing and immunity in certain diseases in the absence of antibodies have been explained in this way.

With the accumulation of information it became increasingly apparent that certain specific phenomena not only cannot be reproduced by the injection of immune serum but differ in many respects from those

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which can be so reproduced. A condition similar to bacterial allergy or to the eczematoid allergic reaction of human skin has never been reproduced by passive immunization. Bacteria usually produce strong immune serum, but the condition produced by the injection of these serums in the organism is very different from bacterial allergy. Besides the immunologic phenomena associated with circulating antibodies, there seems to exist another class with markedly different properties and without direct connection with free antibodies. The latter class acquires particular significance by the fact that the development of the phenomena is often associated with the infectious diseases (bacterial allergy), and healing probably depends in many cases on such phenomena.

As long as these phenomena were observed under complicated conditions only, in cases of actual infectious diseases and of clinical allergy, it was impossible to obtain definite evidence as to whether the differences which separated them from the phenomena transmitted by antibodies were real and important or only accidental. The bacterial antigens are so complex, and during an infection so many different factors influence the reactions of the organism, that the interpretation of the observations has always remained questionable.

The observations which are reviewed later furnish a definite proof for the validity of the distinction between these two classes of immunologic phenomena. A condition corresponding to bacterial allergy was produced with pure, simple antigens, such as crystalline egg albumin and ovomucoid. As the same pure antigen in the same organ may produce a condition corresponding either to bacterial allergy or to the passive immunity of the tissues due to circulating antibodies, the differences between these conditions certainly represent differences in the immunity response. With this observation as a start, it was recognized by gradual steps that the contrast between sensitiveness to tuberculin and the condition produced by passive immunization is not restricted to a few special immunologic phenomena but represents a constant difference between active and passive immunity. Active immunization always produces certain effects in the tissues which are not reproduced by passive immunization. Sometimes the special effects of active immunization are slight and transitory; under other conditions they develop with great intensity, and, as in bacterial allergy, they constitute the dominant part of the immunity response. It was recognized also that certain diseases exert a strong influence on the development of active immunity and that a close connection is present between the immunity response and the anatomic lesions.

In the light of these observations, certain problems of immunology appear in a new form, especially the immunity response during the disease and the conditions of the healing. For this reason it seems indi-

cated that a short systematic review of these observations, the reports of which are scattered in numerous publications, should be prepared and an effort be made to evaluate their bearing on the understanding of immunologic phenomena.

ACTIVE VERSUS PASSIVE IMMUNIZATION

When a protein antigen, such as horse serum or egg white, is injected into a guinea-pig, the first demonstrable specific effect, according to the current belief, is anaphylactic sensitiveness. This may develop as early as the fifth day, though usually it does not appear until the seventh. Antibodies, demonstrable by the precipitin reaction or by the power to transfer anaphylactic sensitiveness passively, do not usually appear until a few days later, and the difference in the time of development is attributed to the imperfection of the methods used in demonstrating small amounts of antibodies.

In contrast to this my associates and I have been able to show that antigen-specific reactions of the skin can be obtained with great regularity at a distinctly earlier period than that at which anaphylactic shock appears. Guinea-pigs given injections of a few milligrams of egg white or horse serum show a positive cutaneous reaction on the fourth day after injection.[1] If turtle egg is used, positive cutaneous reactions are rarely observed on the fourth day but are regularly present on the fifth.[2] These early cutaneous reactions deserve special attention, as they differ in many respects from those in a later period of immunization (several weeks after treatment) and from the reactions in passively sensitized animals. The early reactions of the skin are similar to slight reactions to tuberculin, as they develop only after a period of incubation of several hours and persist for two days or longer. In passively sensitized animals, on the other hand, reactions of this type are never observed. However, the dose of sensitizing serum or the dose of antigen employed in making the cutaneous tests is varied and whether such different antigens as crystalline egg albumin, egg globulin or an extract of tubercle bacilli are studied, the reaction of the skin always remains a quickly developing edematous wheal.[3] Histologic studies, moreover, of the two types of cutaneous reactions, the slight early reactions and the reactions of the passively sensitized animals, show characteristic differences in their microscopic structures.[2b] This indicates that they are the result of two different mechanisms. The slight early reactions in

1. (*a*) Dienes, L.: Proc. Soc. Exper. Biol. & Med. **28**:75, 1930; (*b*) Dienes, L., and Mallory, T. B.: Am. J. Path. **8**:689, 1932.

2. Dienes, L., and Simon, F. A.: J. Immunol. **28**:321, 1935.

3. (*a*) Dienes, L.: J. Immunol. **14**:43, 1927; (*b*) **15**:153, 1928. (*c*) Dienes and Mallory.[2b]

actively sensitized animals are characterized by a slowly developing but finally dense cellular infiltration in which mononuclear cells predominate, whereas in slight reactions in passively sensitized animals dilatation of blood vessels and exudation of serum, followed by varying degrees of infiltration of polymorphonuclear cells, are observed.

The early cutaneous reactions are the only manifestation of the specific response during the fourth, fifth and sixth days. Later anaphylactic shock can be obtained; precipitins may appear in the serum, and the cutaneous reactions gradually take on the form characteristic of passively sensitized animals.[4]

It is apparent from this description that the first manifestation of the specific response to an antigen is not the appearance of antibodies in the circulation and their diffusion through the tissues but a type of hypersensitiveness of the tissues which cannot be reproduced by passive immunization. The difference between this early sensitiveness of the tissues and that transmitted by passive immunization is not quantitative. The development of cutaneous reactions, their macroscopic appearance and their histologic structure differ. They represent two specific mechanisms, the one being characteristic of active and the other of passive immunization. These two types of reactions have nothing to do with the chemical nature of the antigens, because both can be observed with the same pure antigen, i. e., crystalline egg albumin.

Reactions of the early preanaphylactic type in otherwise normal noninfected animals always remain relatively inconspicuous, and for this reason probably they have not been previously observed; 0.1 mg. of egg white after an incubation period of twenty-four hours usually produces only a bright red, slightly swollen spot from 10 to 15 mm. in width on the fifth or sixth day after the first inoculation. If the development of the immunization process is examined in tuberculous guinea-pigs, one finds that the intensity of the cutaneous reaction under appropriate conditions increases considerably on the sixth day or later and that 0.1 mg. of egg white (occasionally even as little as 0.02 mg.) produces a large necrotic reaction.[5] That these severe necrotic lesions are essentially only intensified forms of the early reactions of uninfected animals is indicated by several important points of similarity: (1) the delayed appearance, (2) the long duration and (3) correspondence, both grossly and microscopically, between the slight reactions which can be obtained with a few thousandths of a milligram of egg white, even in animals which show necrotic reactions with larger doses, and the early reactions. Moreover, when necrotic cutaneous reactions first appear in tuberculous guinea-pigs, precipitins are often absent from the serum, and a guinea-

4. Dienes, L.: J. Immunol. **21**:221, 1931.

5. (*a*) Hanks, J. H.: J. Immunol. **28**:105, 1935. (*b*) Dienes.[3b]

pig which gives a reaction of this type to a few hundredths of a milligram of egg white sometimes is not affected by the intravenous injection of large doses of the same antigen.[4]

This extreme degree of hypersensitiveness of the tissues develops only after active sensitization and in infected animals. It is entirely independent of circulating antibodies and is never observed in passively sensitized guinea-pigs. In a study of passive sensitization in guinea-pigs use has been made of the fact that in tuberculous guinea-pigs repeated injections of egg white produce precipitating serum equal in strength to the strongest rabbit serum. As much as 20 cc. of such serum was injected into several guinea-pigs.[3b] When they were tested one or two days later they showed only the characteristic quickly developing anaphylactic type of reaction. The center of the lesion was at times hemorrhagic; the hemorrhage, however, in contrast to that of the tuberculin type of reaction, developed in a few minutes and usually was resolved later without permanent injury to the tissue.

When this early type of preanaphylactic hypersensitiveness, which has just been discussed, is compared with the ordinary hypersensitiveness to tuberculin of guinea-pigs suffering from tuberculous infection, it is found that they correspond in the following essential points: (1) lack of relationship to circulating antibodies, (2) time relationships of delayed development and protracted duration, (3) macroscopic and microscopic pictures and (4) intensifying action of an active tuberculous infection. It is evident that hypersensitiveness to tuberculin, the classic example of bacterial allergy, corresponds in every respect to the early phase of sensitization and, in fact, consists merely of a particularly intense and lasting form thereof.

Both the sensitiveness of the skin to tuberculin after a heavy infection with tuberculosis and the sensitiveness to egg white, if this substance is injected into a tuberculous lesion, increase rapidly in intensity at the end of the first week without changing their character. It could not be decided whether this depends on a purely quantitative increase in strength or on a qualitative alteration in the sensitiveness. It may be caused by the extension of the hypersensitiveness to the epithelial layer of the skin.[6] It is remarkable also that the anaphylactic type of cutaneous sensitiveness is much stronger after active than after passive immunization, however intensive the latter may be. In actively sensitized guinea-pigs 0.1 mg. of egg white may produce a large edematous area 80 mm. in diameter, while the serum of these animals gives only a trace of precipitation. If the precipitin content of the serum is strong, the areas of reaction are smaller, but a hemorrhagic center develops. In comparison with this, as has previously been mentioned, guinea-pigs

6. Dienes, L.: J. Immunol. **24**:253, 1932.

passively sensitized with large doses of serum show after injection of 0.1 mg. of egg white only a moderate reaction without hemorrhage. Furthermore, only slight hemorrhage is observed in the cutaneous reactions produced by injection of 0.5 mg. of egg white. Passive sensitization reproduces the anaphylactic type of cutaneous sensitiveness in its typical form but as compared with active sensitization reproduces it only in a relatively slight degree, even if excessive doses of serum are used. Observations made on rabbits show an even greater difference between the strength of the anaphylactic response in actively immunized animals and that in passively immunized animals. It has been observed in cases of foot and mouth disease that the passive immunity conferred by large doses of serum is never comparable to a strong active immunity.[7] It is possible that the anaphylactic type of tissue sensitiveness, like the tuberculin type, is due to active immunization of the tissues and not to the diffusion of antibodies through them. The observations just made, though their meaning cannot be ascertained positively, indicate that the process of pure tissue immunization, the production of free antibodies not being included, probably passes through several distinct phases.

In rabbits the immunization process follows the same course as that in guinea-pigs.[1b] On the fourth day after the first injection, we obtained a slight delayed type of cutaneous reaction, histologic sections from the area of which showed infiltration mainly with mononuclear cells. The delayed type of reaction in rabbits, either to protein antigens or to tuberculin, remains permanently slight. In contrast, the anaphylactic type of cutaneous reaction produced with certain protein antigens is very strong. The classic Arthus phenomenon, produced by repeated injections of large doses of horse serum, according to the histologic studies of Opie [8] and Gerlach,[9] corresponds to the anaphylactic type of cutaneous reactions. Tuberculous rabbits treated with injections into the tuberculous lesions exhibit reactions of the skin which may be very strong (an area of necrosis of 3 cm. with 0.5 mg. of egg white) at the time when the precipitin reaction is still slight; these reactions, though corresponding to the anaphylactic type, as I have already stated, are probably the result of active immunization of the tissues.

Observations made on human beings are in complete agreement with those on guinea-pigs. Jones and Mote [10] recently described the accidental sensitization of children with very small doses of rabbit serum. The first reactions of the skin were always of the delayed type. The sensitization of man to guinea-pig serum was carefully studied by

7. Maitland, H. B.: A System of Bacteriology, London, 1930, vol. 7, p. 73.
8. Opie, E. L.: J. Immunol. **9**:259, 1924.
9. Gerlach, W.: Virchows Arch. f. path. Anat. **247**:294, 1923.
10. Jones, D. T., and Mote, J. R.: New England J. Med. **210**:120, 1934.

Simon and Rackemann.[11] They, too, found that the first cutaneous reactions were always delayed. In certain cases, positive reactions of the skin were obtained as early as the fourth day after treatment. Very small doses of serum (less than 0.01 mg. of protein) were sufficient to produce definite sensitiveness of the skin. If these small doses were repeatedly given, the reactions remained of the delayed type for several weeks. The sensitiveness sometimes attains a high degree of intensity. Simon and Rackemann observed after injections of 0.1 cc. of a 1:100 dilution of guinea-pig serum (containing about 0.1 mg. protein) areas of delayed reaction 40 mm. in diameter, which persisted for several days. Sooner or later, depending to a large extent on the dose of injected serum, the type of sensitiveness of the skin changed, and the reactions acquired the character of the immediate response. All these investigators (Jones and Mote and Simon and Rackemann) succeeded in transferring the sensitiveness passively at this stage and observed only immediate reactions at the sites of passive sensitization. Precipitins and complement-fixing antibodies were not found in the blood serum after treatment with small doses of antigen. In man the phase represented by delayed reactions is stronger and lasts longer than in guinea-pigs or rabbits. This is probably in conformity with the tendency to the development in man of exceptionally strong sensitiveness to tuberculin.

One important characteristic of the process of sensitization, which has not so far been clearly observed in guinea-pigs or rabbits, is apparent in man, in whom sensitiveness sometimes remains localized at the site of the injection and for a considerable period no general sensitiveness develops. Redfern[12] described cases of this condition as instances of the delayed type of reaction; Simon and Rackemann, as instances of immediate reaction. It is the usual experience in man, as in animals, that after treatment with even very small doses of antigen sensitiveness develops in the whole skin at the same time as at the site of the injection. The conditions on which the development of the localized sensitization depends are not yet known. Another type of localized sensitization, the exclusive sensitization of the skin without development of general sensitiveness, is the rule in hypersensitiveness to poison ivy and Primula and in other similar conditions, both in man and in guinea-pigs. In these cases the hypersensitiveness is probably localized in the epithelium. In animals selective sensitization of the eye and of the subarachnoid space has been observed. Under appropriate conditions not only sensitization but the production of free antibodies may be shown

11. (*a*) Simon, F. A., and Rackemann, F. M.: J. Allergy **5**:439, 1934. (*b*) Rackemann, F. M.: ibid. **5**:617, 1934.

12. Redfern, W. W.: J. Immunol. **18**:109, 1930.

to start as a local process in the tissues directly affected by the antigen. Smith, Orcutt and Little,[13] for instance, described the local production of antibodies in the udders of cows inoculated with Brucella abortus, and McMaster and Hudack [14] observed that after injections of bacteria into the ears of mice agglutinins appeared first in the corresponding lymph nodes and for a while were present in higher concentration there than in the serum or in extracts of other lymph nodes. A few well controlled positive observations, in my opinion, are sufficient to prove the occurrence of local immunity reactions, even if, as a rule, the immunity response develops generally and the conditions on which its local development depends are so far unknown.

Briefly, the result of this discussion may be stated as follows: Active immunization, even with pure protein antigens, such as crystalline egg albumin, produces a condition which cannot be reproduced by passive immunization. This condition is a pure tissue hypersensitiveness, characterized by delayed and protracted cutaneous reactions. In microscopic section the lesions show infiltration mainly with mononuclear cells. This sensitiveness develops soon after treatment; it is slight in guinea-pigs and rabbits and is stronger and persists longer in man. Under the influence of certain diseases this phase of the immunity response attains a high intensity. The well known sensitiveness to tuberculin is an example of this process. In guinea-pigs and rabbits antibodies appear usually at the beginning of the second week after the injection of a substance, such as egg white. Their appearance is accompanied by susceptibility to acute anaphylactic shock and by a characteristic change in the cutaneous reactions, which become immediate and evanescent and consist of exudation of serum and polymorphonuclear leukcoytes. The conclusion that the early preanaphylactic hypersensitiveness and bacterial allergy depend on active immunization and not on passive distribution of antibodies is not based alone on such negative evidence as the inability to demonstrate antibodies, to produce anaphylactic shock or to accomplish passive transfer. Such negative evidence in itself is not conclusive. The main support of the conclusion is the observation that passive immunization produces always a condition qualitatively different from the early hypersensitiveness and from bacterial allergy. There are two groups of phenomena, differing from each other in many important characteristics, one of which is produced exclusively by active immunization while the other appears during the development of immunity response together with the antibodies and can be easily transferred passively. The observations made in rabbits also

13. Smith, T. H.; Orcutt, L. M., and Little, L. B.: J. Exper. Med. **37**:153, 1923.

14. McMaster, P. D., and Hudack, S. S.: J. Exper. Med. **61**:783, 1935.

suggest that the second phase of hypersensitiveness does not depend entirely on the diffusion of antibodies through the tissues but is probably based largely on active sensitization. It is probable that the process of immunization is more complicated than indicated here and that both the introductory sensitiveness of the tissues and the production of antibodies may consist of successive phases or of different processes running parallel to each other.[15]

Considerations concerning the nature of specificity make it probable that all antigen-specific phenomena, no matter how different in other respects, are produced by an essentially similar response of the organism. It is improbable that such fine adjustment to the chemical structure of the antigen as is necessary to produce specific reactions should depend on several independent mechanisms. Many observations, also, to which I have referred indicate that bacterial allergy and the production of antibodies are closely related phenomena. They may represent successive phases of the same process. Personally, I prefer not to form a definite hypothesis concerning their relationship. The following considerations suggest, in my opinion, the most probable explanation:

It is generally believed that antibodies may remain, after their production, fixed on the cells and that they do not necessarily enter the circulation. It is possible that the antibodies remain at first in connection with the cell constituents which produce them and do not appear on the surface of the cells. Passively introduced antibodies do not come into a similar relationship to the cells. While the antibodies are exclusively inside the cells, the multiplication of these cells, capable of specific reaction and not a vascular reaction, would be the reasonable response to the antigen. Bacterial allergy may represent a phylogenetically older stage in the development of specific response, which later was supplemented by the extension of the specific activity to the humors. Another possibility which must be taken into account is that active and passive treatment may sensitize different tissue elements. Similar interpretations of sensitiveness to tuberculin agree well with the observations, but it must be kept in mind that the interpretations in themselves have no importance. In this case only the observation that active immunization produces a condition which cannot be reproduced by passive immunization is important.

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15. Marked differences exist between the antibodies of immune serum and those observed in cases of hay fever in man. These antibodies seem to react with the antigen only in connection with the tissues. Similar antibodies are produced in cases of infestation with worms, and the antibodies in certain virus diseases present many analogies to them. The cause and significance of the special properties of these antibodies are one of the most interesting problems of immunology.

The conception of the process of immunization just described originated in the differentiation of the anaphylactic and the tuberculin type of cutaneous reactions by Zinsser.[16] The validity of this differentiation is not generally accepted. It is believed, however, that our observations have furnished such simple and definite experimental evidence that it is not necessary to discuss the objections which were formerly raised against it (Doerr[17]). I shall, however, briefly refer to a few observations which seem to contradict our opinions.

Recently, several authors have described the development of necrosis in cutaneous reactions in guinea-pigs. It was thought that these reactions presented analogies to tuberculin reactions and that they might cause confusion in the interpretation of the sensitiveness to tuberculin. Seibert[18] described necrotic cutaneous reactions in guinea-pigs treated intensively with the protein substances of tubercle bacilli. These reactions correspond to those of the anaphylactic type, and the fact that the cutaneous tests were made with 15 mg. of a preparation of tuberculin which in a hundred and fifty thousandth of the amount (0.0001 mg.) produces strong reactions in tuberculous guinea-pigs makes it impossible that the guinea-pigs possessed an appreciable amount of sensitiveness to tuberculin. Slight reactions shortly after the first injection of the protein substances of the tubercle bacillus are, according to our observations, similar in every respect to slight reactions to tuberculin. After more intensive treatment the reactions take on an anaphylactic character. As compared with the reactions to the amounts used in the cutaneous tests by Seibert, guinea-pigs possessing a strong tuberculin type of hypersensitiveness to egg white often show strong necrotic cutaneous reactions with 0.02 mg. of egg white.

Kellett[19] reported that necrotic reactions of the skin develop in guinea-pigs given intraperitoneal injections of a large dose of horse serum when they are later subjected to cutaneous tests with strong antihorse rabbit serum. He attributed the development of necrosis to the high concentration of the antibodies. I repeatedly made similar experiments with egg white and antiegg white guinea-pig serum obtained from tuberculous guinea-pigs and also with antiegg white rabbit serum. The reactions always remained of the anaphylactic type. It is, however, in accordance with our experience that if the guinea-pigs possess strong precipitating serum, hemorrhages occur regularly in cutaneous reactions of the anaphylactic type. If doses larger than 0.1 mg. are

16. Zinsser, H.: J. Exper. Med. **34**:495, 1921; Resistance to Infectious Diseases, New York, The Macmillan Company, 1931.

17. Doerr, E., in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1929, vol. 1.

18. Seibert, F. B.: J. Infect. Dis. **51**:383, 1932.

19. Kellett, C. G.: J. Path. & Bact. **33**:981, 1930.

used in the tests, partial necrosis sometimes develops in the hemorrhagic area. Reactions obtained with small test doses in these animals correspond in every respect to those of the anaphylactic type. The hemorrhagic reactions correspond to the Arthus phenomenon in rabbits and have nothing to do with the tuberculin type of hypersensitiveness.

Shwartzman described experiments [20] in which, by repeated injections of antigen in the same sites, large necrotic reactions were produced in sensitized rabbits. It is impossible to tell whether these observations represent a real analogy to the development of necrosis in reactions to tuberculin. Necrosis, however, is not the most characteristic property of the tuberculin type of cutaneous reaction and is not sufficient to differentiate it from other reactions of the skin.

Recently Ramon and Richou [21] made a study of one of the most important points under consideration—the development of active local immunity. Many years ago Römer,[22] studying the development of immunity following instillation of abrin into the eye, observed that at first local immunity develops in the treated eye. The immunity in the eye which was not treated and general immunity, both of which depend on circulating antibodies, develop later. Ramon and Richou repeated these experiments with abrin and with diphtheria and staphylococcus toxin and obtained negative results. The immunity became noticeable always simultaneously in both eyes and depended on the appearance of antibodies in the blood. The authors concluded that a local tissue immunity independent of circulating antibodies does not exist. Such observations may awaken doubt as to the significance of our results with egg white. On closer examination, however, they do not contradict either our observations or those of Römer. In the experiments of Ramon and Richou, from six to eight instillations were needed, requiring four weeks or more, before immunity was noticed. Under such conditions the production of antibodies always predominates in the immunity response. The experiments were made with rabbits; in these animals reactions of the tuberculin type are observed only for a short period, from three to six days, after a single injection of egg white. In Römer's paper two instances were described in which local immunity developed in a rabbit in the eye which was treated. In both instances this was observed at the second instillation, eleven and eighteen days, respectively, after the first. Antitoxic immunity develops slowly, and its intensity after a single treatment is slight; experiments with toxins are less favorable for the study of the development of the process of immunization than experiments with egg white. However, the development of

20. Shwartzman, G.: J. Exper. Med. **57**:859, 1933.

21. Ramon, G., and Richou, R.: Ann. Inst. Pasteur **54**:518, 1935.

22. Römer, P.: Arch. f. Ophth. **52**:72, 1901.

bacterial allergy indicates that during the infectious diseases the bacterial antigens are capable of producing in a few days a strong active immunity response.

In order to give a clearer conception of the nature of the experimental evidence which supports our conclusions, a few selected protocols of the actual experiments are included. In addition to our own results the papers especially of Lewis and Loomis,[23] Hanks,[5a] Laporte [24] and Simon and Rackemann [11] contain observations directly related to the problem under discussion.

Table 1, taken from a paper by Mallory and me,[1b] shows the characteristics of early cutaneous reactions. This table was selected because it indicates clearly the specificity of the reactions.

TABLE 1 (*from Dienes and Mallory* [1b]).—*Four Hour and 24 Hour Readings of Skin Tests on Uninfected Guinea-Pigs 6 Days After Sensitization with Egg-White or Horse Serum*

	December 22	Skin tests December 28				
		Egg-white 0.2 mg.		Horse serum 0.005 cc.		Tuberculin
Guinea pig No.	Sensitization	4 hr. reading	24 hr. reading	4 hr. reading	24 hr. reading	24 hr. reading
68	5 mg. egg-white i.p.	Neg.	10×10 red	Neg.	Neg.	Neg.
69	"	Neg.	20×22 red	Neg.	Neg.[1]	Neg.
70	0.1 cc. horse serum i.p.	Neg.	Neg.	Neg.	12×10 red	Neg.
71	"	Neg.	Neg.	Neg.	14×12 red	Neg.[1]

[1] These animals showed a trace of redness about the puncture wound.
This experiment was twice repeated with similar results, both grossly and histologically. For histological purposes these animals were killed 24 hours after skin testing. In other similarly treated animals, not sacrificed, the area of induration and redness persisted 48 hours before beginning to fade. Delayed and prolonged reactions of this type have been obtained as early as the third day after injection.

The following description accompanied the table:

Microscopically these lesions show at six hours a marked infiltration with mononuclear cells. This is particularly marked in the immediate subepithelial layer and also in the loose tissue between the corium and the muscularis. Polymorphonuclears may be almost absent or present in moderate numbers, the usual formula being about 80 to 90 per cent mononuclears to 20 to 10 per cent polymorphonuclears. In rare instances the latter may rise almost to 50 per cent but never predominate. In the control reactions the infiltration is very much less extensive and polymorphonuclears make up 60 to 80 per cent of the invading cells.

At 24 hours the infiltration is much more intense and averages 85 to 90 per cent mononuclears. No necrosis was observed in these reactions except in the line of the needle puncture.

23. Lewis, P. A., and Loomis, D.: J. Exper. Med. **40**:503, 1924.

24. Laporte, R.: Ann. Inst. Pasteur **53**:598, 1934.

Table 2 records the observations in instances of the strong delayed type of cutaneous reaction to injections of egg white in tuberculous guinea-pigs.[3b] The animals were inoculated with 0.01 mg. of virulent tubercle bacilli in both groins. After two weeks 0.2 mg. of egg white was injected, first into the tuberculous lesion on the right and two days later into that on the left. The sensitiveness of the skin was tested after seven days. Two days after the cutaneous test the serum of guinea-pig 5 gave no precipitation with egg white, and that of guinea-pig 6, a very slight precipitation.

TABLE 2.—*Cutaneous Reactions of the Tuberculin Type with 0.1 Mg. of Egg White*

Time After Injection	Guinea-Pig 5	Guinea-Pig 6
20 min.	No reaction	No reaction
1 hr., 20 min.	No reaction	No reaction
6 hr.	Very slight redness and swelling, 15 by 15 mm.	Slightly red swelling, 18 by 15 mm.
24 hr.	Large swelling, 20 by 16 mm.; violet-white area, 9 by 7 mm., surrounded with red	Very large swelling, 25 by 25 mm.; violet-white area, 10 by 12 mm., surrounded with red
48 hr.	Medium red swelling, 16 by 15 mm.; necrosis, 8 by 8 mm.	Very large red swelling, 25 by 25 mm.; necrosis, 15 by 15 mm.

TABLE 3.—*Cutaneous Reactions in Passively Sensitized Guinea-Pigs*

	Cutaneous Reactions of Guinea-Pig 1 to		Cutaneous Reactions of Guinea-Pig 2 to	
Time After Injection	0.1 Mg. Egg White	0.5 Mg. Egg White	0.1 Mg. Egg White	0.5 Mg. Egg White
1 hour (the highest development of the reaction)	Large soft swelling, 20 by 18 mm. about red area, 9 by 9 mm.	Soft swelling, 23 by 18 mm. about deep violet area, 13 by 12 mm.	Slight swelling, 16 by 13 mm. about slightly red area, 9 by 9 mm.	Large soft swelling, 22 by 18 mm. about violet-red area, 13 by 11 mm.
24 hours	Red spot, 7 by 7 mm.	Very slight swelling, 30 by 26 mm. about red area, 10 by 10 mm.	Slightly red spot, 10 by 10 mm.	Red spot, 12 by 10 mm.
48 hours	No reaction	Small red spot	No reaction	No reaction

Similar cutaneous reactions to egg white and tuberculin show essentially the same microscopic structure as the early reactions to egg white. They start with infiltration of mononuclear cells, which becomes marked after six hours. Edema, necrosis of the tissue and infiltration with polymorphonuclear cells develop later in proportion to the symptoms of acute inflammation. In very slight reactions, produced by minute doses of antigen, infiltration with mononuclear cells is predominant through the whole course of the reaction.

The effect of passive sensitization is shown in table 3.[3b] Guinea-pig 1 was given injections of 21 cc. of strong antiegg white serum obtained from tuberculous guinea-pigs. The injections were distributed

over three consecutive days, and one half of the serum was injected intravenously. Guinea-pig 2 received 5 cc. of the same serum. The guinea-pigs were given cutaneous tests the day after the last injection of serum.

The microscopic structure of areas showing similar cutaneous reactions of slighter intensity was described as follows [1b]:

> The microscopic appearances were quite different from those of the tuberculin tests. At 1 hour the blood vessels were dilated, the corium showed a marked diffuse edema, and polymorphonuclears were scattered in large numbers throughout the tissue. No increase in mononuclear elements could be made out.
>
> At 6 hours the congestion and edema had slightly decreased. The polymorphonuclear infiltration on the other hand was more dense and a small number of large mononuclears had appeared. At 24 hours almost no trace of reaction was left except for a few scattered mononuclears.

The influence of tuberculous lesions on the development of the sensitiveness of the skin is indicated in the following experiment [25]:

> Fourteen large guinea-pigs were given injections of 4 mg. of tubercle bacilli in both testicles (the slightly virulent strain RI being used). Two days later five of the group were given intravenous injections of from 0.2 to 0.6 mg. of egg white, and the remaining nine animals, injections of the same dose into the fresh tuberculous lesions in the testicles. When the pigs were given cutaneous tests two weeks later with 0.1 mg. of egg white, those treated intravenously gave slight reactions of the anaphylactic type, which did not differ from the reactions of nontuberculous guinea-pigs sensitized by intravenous injections. Seven of the nine guinea-pigs treated with intratesticular injections gave large necrotic cutaneous reactions of the delayed type, similar to those described in table 2. In the remaining two animals the reactions were of the same type but were less strong.

It must be mentioned that the result of sensitization of tuberculous guinea-pigs is not always so uniform. A procedure which gives good results in many experiments may in others be without effect. A similar but more pronounced variability of results has been observed in the sensitization of guinea-pigs with neoarsphenamine.[26] This variability, in my opinion, does not detract from the significance of positive results, and it may even be of importance by attracting the attention to certain conditions which exert a great influence on the immunity response.

The development of the immunity response in man is illustrated by table 4, taken from a paper by Simon and Rackemann.[11a]

The authors stated: "The table indicates clearly enough that repeated intracutaneous injection of 1:10 dilution of guinea pig serum results in the prompt and regular development of at first delayed and then immediate skin reactions." After treatment with higher dilutions of guinea-pig serum (1:100 and 1:1,000), the delayed type of reaction persisted longer.

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25. Dienes, L.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **68**:13, 1930.
26. Sulzberger, M. B., and Simon, F. A.: J. Allergy **6**:39, 1934.

THE SPECIFIC IMMUNITY RESPONSE IN INFECTIOUS DISEASES

The study of the immunity reactions in the course of the natural infectious diseases offers many difficulties. A few may be mentioned as follows: In many cases the infectious agent cannot be cultivated; a disease corresponding to the disease in man cannot be produced in animals; the antigenic structure of bacteria is complex and is not sufficiently known; nonspecific factors influence the manifestations of the immunization, and the study of the cutaneous reactions does not necessarily give adequate information about the immunization of inner organs, etc. As the present information is fragmentary and every

TABLE 4 (*from Simon and Rackemann* [11a]).—*Reaction to Repeated Intracutaneous Injections, 0.10 Cc. Each, of Guinea-Pig Serum Diluted 1:10 in Atopic Patients*

				Weeks														
	Patient	Age	Diagnosis	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1.	T. W.	26	Asthma V. M. R.	O	X	X	X	X	13	16	19									
2.	J. S.	25	Asthma	O	X	XX	18	22												
3.	S. D.	47	Asthma	O	X	XX		XX	11		15		18							
4.	M. B.	52	Asthma	O	X	XX		XX	12	9	18	13	16	13		17				16
5.	L. W.	46	Asthma	11	9	8	9	7		11				13				15		
6.	H. B.	12	V. M. R.	O	O	O	O	O	O	O	13									
7.	L. N.	43	Asthma	O	XX		16	15	15				25							15
8.	J. L.	35	Asthma	O	XX		12	11	X	XX	12		11					13		
9.	E. L.	23	Atopic eczema	O		O		O	10	9		13		15		16				
10.	G. F.	50	Asthma	O	O	X	X	X	12	10	14	17	16							
11.	F. B.	48	Asthma	O	X	XX		XX	12				10	10	11	12		16		
12.	J. P.	20	V. M. R.	10	11	13		12	13				15					17		
13.	S. D.	21	Asthma	X	XX	XX	20	25	20		17									
14.	S. E.	54	Asthma	O	XX	XX				O				XX			9	11	13	
15.	M. O.	48	Asthma	O	XX	10	XX	10												
16.	H. S.	22	H. F.	10				11			20									

Delayed reactions are expressed as O, X or XX according to the patient's story or as actual measurements in millimeters if observed by us. Immediate reactions are expressed by the arabic figures which indicate the average diameter of the wheal in millimeters.

disease presents an individual problem, the consideration must be limited to broad outlines. In the discussion which follows I have had in mind mainly such diseases as tuberculosis, typhoid, pneumonia and smallpox. The experimental infections of small animals are different in many respects from natural diseases and usually allow the study of only certain phases of the immunity process.

One of the striking characteristics of the immunity response in the infectious diseases is the development of bacterial allergy,[27] to which Coca gave the name "hypersensitiveness to infection." It is strongly

27. The terms bacterial allergy and tuberculin type of sensitiveness are used interchangeably. The term bacterial allergy is accepted in referring to infectious diseases. The term tuberculin type of sensitiveness is more appropriate for designating a similar sensitiveness to egg white and the early slight cutaneous sensitiveness in normal animals and man.

developed in various diseases, such as tuberculosis, Br. abortus infection, chronic glanders, fungous infections, inguinal lymphogranulomatosis and typhoid. In guinea-pigs I observed this type of hypersensitiveness after infection with smallpox vaccine (unpublished observation). Among these infectious conditions there are chronic and acute and bacterial and virus diseases. The hypersensitiveness develops early in the course of the disease and usually attains high intensity. It persists during the whole course of the disease and disappears soon after healing. In guinea-pigs, after a heavy infection with tubercle bacilli, the sensitiveness of the skin is sometimes already noticeable on the fourth day. It can be stated that in many diseases the bacterial allergy, which is the most salient characteristic of the active immunization and which cannot be reproduced by passive immunization, is strongly developed.

Information about the frequency of the development of bacterial allergy in the different infectious diseases is inadequate. In most virus diseases there is no means of testing the hypersensitiveness, and probably also in bacterial diseases often inadequate preparations have been tried. The skin does not necessarily give satisfactory information concerning the development of hypersensitiveness, and it is known that in several diseases the ability of the skin to react is temporarily depressed. The present methods are so imperfect that the demonstration of hypersensitiveness in many diseases is more significant than its apparent absence in others.

If the production of antibodies during the course of the disease is examined the same variation is found as in the case of bacterial allergy. In certain diseases, though strong immunity develops, antibodies are not produced, or they are produced only after artificial hyperimmunization. Often in similar diseases the production of antibodies differs. For instance, in tuberculosis antibodies are hardly ever produced (the complement fixation of the serum depends mostly on nonspecific factors); in brucella infection agglutinins are usually produced in high titer. In the same disease the production of antibodies may be variable. In diseases which run a longer course, such as typhoid, the antibodies appear during the course of the disease, and in others, usually only after healing. An interesting characteristic of the production of antibodies is the great increase resulting from vaccination or repeated infections. In tuberculous guinea-pigs during the first week after infection, antibodies as a rule are not demonstrable in the serum, but if small doses of tubercle bacilli (a few thousandths of a milligram) are injected into the tuberculous lesions, the serum gives a specific complement fixation in high dilution (1:3,000 or higher). The effect of hyperimmunization by repeated injections of virulent material on the production of preventive antibodies in virus diseases is well known. The ability of the organism to produce circulating antibodies is utilized only

slightly during the healing of the disease, in marked contrast to the intensive development of the tuberculin type of sensitiveness. The great influence which the artificial injection of virulent material exerts on the production of antibodies suggests that the purpose of antibodies is rather the prevention of a new distribution of virulent material from persisting foci than the healing of the disease.

The immunity response has been thoroughly studied with modern methods in cases of pneumonia. The tuberculin type of hypersensitiveness develops during the disease to the nucleoprotein fraction of the pneumococcus and to the so-called C substance, and it disappears soon after healing. The immunity and the protective antibodies which appear in the serum are seemingly connected with the capsular carbohydrate antigen. After the crisis this antigen often produces an anaphylactic type of cutaneous reaction. We do not believe that these observations indicate an essential difference between the various types of antigens in their relation to the tuberculin and anaphylactic types of sensitiveness, because we could produce either type of response without difficulty with pure protein antigens. The protective antibodies usually appear in the serum after the crisis, but sometimes before it. The rôle of the antibodies in the production of a crisis remains doubtful, however, since artificially injected protective antibodies do not necessarily introduce a crisis. Of great importance is the observation [28] that a slight modification in the preparation of carbohydrate antigens thoroughly changes their immunologic properties, showing the difficulties involved in this type of research. It is possible that the purified antigens are different from the antigen complexes which are really responsible for the immunity reactions in the disease and that the special position of the carbohydrate antigens in relation to the tuberculin and anaphylactic types of hypersensitiveness is more apparent than real.

The general impression on the basis of this short review is that in the immunity response during the infectious diseases active immunization plays the preponderant rôle and that the diffusion of antibodies through the tissue fluids probably in many diseases plays only a secondary part. That part of the immunity response which cannot be reproduced by passive immunization is often strongly developed. Productive antibodies occasionally are entirely absent; their amount and the time of their appearance are variable, and often their amount can be strongly increased by a relatively slight treatment. In the natural disease the preponderance of active immunity can be expected; this preponderance, however, acquires a new significance by the observations already made, which show that the effects of active and those of passive immunization are essentially different.

28. Avery, O. T., and Goebel, W. T.: J. Exper. Med. **58**:731, 1933.

SIGNIFICANCE OF THE IMMUNITY RESPONSE

In the preceding sections the development of the immunity response has been described through two successive phases, the first of which, corresponding to the period of active immunization of the tissues, is strongly developed in many infectious diseases and has come to be known as bacterial allergy. The most important question to be considered is at what point in the development of the immunity response healing begins and the disease process ends.

Even a superficial consideration of a few infectious diseases shows that there is no general rule in this respect. Healing may or may not occur at any point in the immunity response. Certain patterns may, of course, be recognized. Acute diseases of short duration, such as vaccinia or pneumonia, show evidence of healing during the first phase of the immunity process before antibodies are demonstrable; in self-limited diseases of longer duration, such as typhoid, the disease process commonly persists for a long period after antibodies are produced, while in chronic diseases, such as tuberculosis and brucellosis, healing bears no direct relation to the specific immune process and, in fact, may be apparent in one area while the disease is actively progressing in another. One must conclude that healing in infectious diseases depends on multiple factors, among which specific and nonspecific elements are of variable relative importance and that, to a large extent, each disease presents an individual problem.

It is at present impossible to give a systematic account of the different specific and nonspecific processes which succeed each other in the course of the disease and which end in the healing. The most important task is, at present, to distinguish these processes and the nature of their respective influences.

In an attempt to assess the relative importance of the several factors there is much to be learned from a comparison of acute and chronic diseases. On the whole, the acute diseases have been much more extensively studied, and for that reason, perhaps, the significance of the second stage of the immunity response, the production of antibodies, has been overemphasized. The protective and antitoxic effects of antibodies, their ability to prevent the spread of infection in certain diseases and their usefulness in therapy are firmly established. Yet it is evident that the healing of natural diseases is not the direct consequence of the appearance of antibodies in the circulating blood. Serum therapy, in fact, through its very limitations furnishes evidence that antibodies are not ordinarily of decisive importance, since the efficiency of serum is usually sharply limited to the period of incubation and to the first few days of the disease. In pneumonia the relationships between healing and the development of antibodies or the effects of immune serum have been intensively studied. Immune serum given a few hours after

the beginning of the disease often prevents its further development and during the first two or three days of the disease exerts a marked influence on its course. Later, even in quantities sufficient to give protective properties to the blood, the immune serum does not exert a marked effect. Moreover, the autogenous protective antibodies which develop in the infected organism do not seem to be closely connected with recovery. Robertson and his associates,[29] in a recent study of the rôle of naturally formed and artificially introduced immune substances, expressed the following opinions: "The appearance" of acquired antipneumococcus immune properties in the serum is "not closely related to recovery. These findings suggest that either the body brings into play more than one mechanism for restraining the spread of the pneumonic process . . . and eventually terminating the infection, or that the elaboration of humoral immune substances represents only one phase of a specific reaction against the pneumococcus." Further, "the chief effect of the injected immune substances is to confine the pneumococci to the pulmonary lesion and to prevent extension of the pathologic process, the actual termination of the disease being occasioned by an unknown process of natural recovery."

In chronic diseases it is apparent that the healing of the established lesions and the immunity to reinfection are, to a large extent, independent of each other and depend evidently on somewhat different conditions. The specific response produces immunity against reinfection, even though it does not succeed in quickly eliminating the disease itself. By vaccination, moreover, the antibody content of the serum can be greatly increased, yet this procedure or the use of therapeutic serum usually has no effect on the duration or outcome of the disease. It is probable that the specific response develops without treatment with such intensity that artificial treatment does not materially increase it. The healing of local lesions depends, however, on the slow prevalence of the healing process over the extension of the disease. This process is influenced not only by the specific immunity but by other factors which cannot be determined at present.

Although acute diseases heal regularly in a certain phase of the disease, the healing is probably a process analogous to that in chronic diseases, and, as was shown in the case of pneumonia, it cannot be regarded simply as the consequence of the development of immunity and antibodies. The specific immunity process has already started during the period of incubation, and it is frequently in an advanced stage when the clinical disease begins. The disease continues to develop

29. Robertson, O. H.; Graeser, J. B.; Coggeshall, L. T., and Harrison, M. A.: J. Clin. Investigation **13**:621, 1934. Robertson, O. H.; Graeser, J. B.; Coggeshall, L. T., and Sia, R. H. P.: ibid. **13**:649, 1934.

in the presence of hypersensitiveness, sometimes also of antibodies, in an organism immune to reinfection, and the clinical symptoms are doubtless caused in part by the immunity response. These conditions are similar to those observed in chronic diseases; in acute diseases, however, the consecutive steps follow each other at such short intervals that analysis is often difficult.

Perhaps the best illustration of the relationship between the disease process and the immunity response was provided by Pirquet's studies of vaccinia.[30] After inoculation a small local lesion develops, which at first is accompanied by little or no general reaction. The immunity response has, however, been developing during this period, and immunity against reinoculation becomes demonstrable on the sixth or seventh day after the primary infection. The clinical disease in vaccinia, characterized by an acute flare-up of the inflammatory reaction at the site of inoculation and by constitutional symptoms, such as fever and leukopenia, does not start until this time, when immunity to reinfection is firmly established. In variola, also, the development of immunity probably begins during the period of incubation, a stage which may be assumed to be analogous to the initial period of vaccinia. Immunity to inoculation with vaccine virus is demonstrable a few days after the appearance of symptoms, yet the variola itself continues to progress in the immune organism and heals at a later stage of the immunity response than the vaccinia.

In typhoid the relapses and the persistence and development of local lesions in the periosteum, bones or gallbladder after healing indicate that the healing is more similar to that in chronic diseases than to the prevention of rapidly fatal septicemia by the administration of antiserum.

Another point of similarity between vaccinia and chronic infectious diseases has been pointed out by Olitsky and Long.[31] They have confirmed the observation that the vaccine virus is not eliminated from the organism with the healing of the lesions but persists for considerable periods thereafter. In their opinion, immunity in rabbits lasts only as long as the virus persists in the organism.

In acute as in chronic diseases the healing of an established infection is more complicated and is accomplished with more difficulty than the prevention of a new infection. The relative importance of the participating factors is probably different in the two processes. It is important to emphasize this because in the study of immunity the prevention of infection in small experimental animals plays an important rôle. It is evident that such experiments do not give information concerning the

30. von Pirquet, C.: Klinische Studien über Vakzination und vakzinale Allergie, Vienna, Franz Deuticke, 1907, p. 197.

31. Olitsky, P. K., and Long, P. H.: J. Exper. Med. **50**:263, 1929.

relative importance of the different immunologic reactions during the actual disease, and in the study of the disease the specific and nonspecific processes characteristic of the disease, such as bacterial allergy, deserve an important place.

When one attempts to study the relationship of bacterial allergy to healing and to immunity produced experimentally, certain difficulties immediately become obvious. Without infection with killed bacteria strong bacterial allergy has been produced with tubercle bacilli only. We made attempts to produce allergy in tuberculous guinea-pigs with various bacteria, employing the technic used with egg white. These attempts remained unsuccessful. A further difficulty is that in the experimental animals the allergy develops in strong form only in chronic infectious diseases, such as tuberculosis and brucellosis. Such diseases are in many respects inappropriate for the purpose. If one were to study the significance of the production of antibodies, for instance, only from the point of view of these two infections, one would be forced to conclude that the production had no significant effect on either healing or immunity. To obtain useful information in regard to the function of antibodies it is necessary to study their development in self-limited acute diseases. Bacterial allergy in tuberculosis or brucellosis cannot, any more than the production of antibodies, be shown to bear a direct relationship to healing. But one is not justified in assuming because of this that in a self-limited disease it may not bear such a relationship. To obtain a true estimate of its significance, one should study it in a self-limited acute disease in which it is well developed. We have found such a suitable subject in infection of guinea-pigs with vaccinia virus.[32]

In the guinea-pig, as in man, marked hypersensitiveness is developed in the course of vaccinia. Histologic study of the areas of cutaneous reaction proved that the hypersensitiveness is of the tuberculin type, since in hypersensitive animals a marked mononuclear infiltration was present. Slight sensitiveness of the skin was probably present from the fifth day after infection, and on the eighth day the sensitiveness was marked. Virucidal antibodies were not observed in the serum until the twelfth day after infection. On the fourth day evidence of healing of the infection was noticeable, but not until the sixth or seventh day was immunity demonstrable in the whole skin. The immunity to reinfection and the healing of the lesions started before antibodies were demonstrable in the serum in the period in which the hypersensitiveness corresponded to the tuberculin type.

From observations made on one disease one cannot draw far-reaching conclusions. They are sufficient, however, to show that only under appropriate experimental conditions can information be obtained on the rôle of the tuberculin type of sensitiveness.

32. Dienes, L., and Naterman, H. L.: J. Immunol., to be published.

In tuberculosis we have recognized an unexpected effect of the sensitiveness to tuberculin, namely, that the sensitiveness exerts a powerful influence on the development of anatomic lesions. Slight reactions of the tuberculin type are characterized, as has previously been stated, by a cellular reaction in which mononuclear cells predominate. As a result of such a reaction the productive inflammation is intensified and accelerated, and if the hypersensitiveness persists for a long period infectious granulomas are produced.

This influence of allergy is readily demonstrated in cases of local serum sickness,[2] a condition produced exclusively by the developing allergy. If the conditions are appropriate at the moment at which the hypersensitiveness appears, an inflammatory reaction develops at the site of injection. This reaction develops before antibodies appear in the circulation in the stage of the immunity process corresponding to that of bacterial allergy. The response of the tissues in these reactions consists mainly of infiltration with mononuclear cells and is similar to early tuberculous lesions.

In work on tuberculosis Mallory and I[32] attempted to obtain closer information concerning the connection between allergy and the development of anatomic lesions. Infection was produced by a large dose of bacilli to insure the rapid development of sensitiveness to tuberculin. In such conditions the sensitiveness of the skin to tuberculin was marked on the fourth day after infection. In a few animals it was noticeable already during the third day. During the first two days only a dense infiltration with polymorphonuclear cells was present around the bacteria injected into the testicle or the groin. On the third day the investment of the lesion with mononuclear cells began, and this process acquired great intensity on the fourth day. The cell type appearing on the fourth day in the reaction of the skin to tuberculin was similar to the cells appearing in large numbers at the site of infection at the same time. It is permissible to conclude that the rapid accumulation of mononuclear cells at each site was due to a common cause, namely, to the development of sensitiveness to tuberculin. The specific tuberculous lesions probably always develop in allergic tissue. They represent the response of allergic tissue to the presence of bacteria and are not produced by special properties of the tubercule bacillus, for example, high resistance to chemical influences and the presence of a certain type of lipoid substances in the bacterium.

An apparent difficulty with this conception is that under natural conditions the sensitiveness of the skin to tuberculin develops later than the typical tubercles at the site of infection. This is probably

32. Dienes, L., and Naterman, H. L.: J. Immunol., to be published.

explained by the local development of sensitiveness to tuberculin in the vicinity of the lesions. In the first section of the paper the observations which support the theory of the local development of the immunity response were referred to, and in work on tuberculosis the observations of Stewart [34] furnished direct evidence for this.

Krause and Peters [35] recognized that sensitiveness to tuberculin accelerates the development of tubercles.

Bacterial allergy may develop within a few days after infection, and hence probably almost from the beginning it exerts an influence on the development of anatomic lesions. In chronic diseases and at the beginning of acute diseases the immunity response is unable to eliminate the infection. Under such conditions the rapid multiplication of certain cell types and the walling off of the foci of infection represent perhaps the only means which the organism possesses to check the progress of infection. The walling off and surrounding of foreign material or injured tissue by appropriate cells are fundamental defensive reactions of the organism. The acceleration of this process is a characteristic effect of bacterial allergy. In contrast to this, circulating antibodies produce quickly developing inflammation with predominance of polymorphonuclear cells.

This effect of the sensitiveness to tuberculin may be of special importance in chronic diseases. The majority of men and also of cattle in infected herds are strongly sensitive throughout life to tuberculin without ever developing clinical disease. In such conditions, which correspond to successful resistance in an infected organism, the effect of sensitiveness to tuberculin probably manifests itself in very slight reactions when a few bacteria are localized in the tissue as a consequence of reinfection or of spread from an old lesion. In tuberculin-sensitive animals the bacteria are surrounded more quickly and more abundantly with mononuclear cells, and the tubercles develop more quickly than in normal animals. It is probable also that the effect of these cells on the bacteria is different from that of normal cells.

The observations which have been reviewed indicate the following points of view concerning the rôle which bacterial allergy plays in infectious diseases: (1) Bacterial allergy is an indicator of active immunization of the tissues; (2) in certain diseases healing and immunity start in this phase of immunity response, and (3) bacterial allergy exerts a powerful influence on the development of anatomic lesions. It is to be hoped that further experimental work along these lines will considerably help the understanding of the disease process.

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34. Stewart, F. W.: Am. J. Path. **1**:495, 1925.

35. Krause, A. K., and Peters, D.: Am. Rev. Tuberc. **4**:551, 1920.

Recently several investigators have claimed that the strong acute inflammatory reaction at the site of localization of the antigen in allergic tissue is of great importance to immunity by localizing the infection and enhancing the defensive reaction. I agree with the opinion of Rich,[36] namely, that direct observations do not support this view. The observations which have been reviewed indicate that the local allergic response to small amounts of antigen is not an acute inflammation but a productive tissue reaction. The quantities of bacteria necessary to produce an acute inflammatory reaction in allergic animals are much larger than the amount of infectious material which transmits the infection. The highest grade of sensitiveness which is observed in man is the sensitiveness to horse serum or to drugs. A man may give a noticeable cutaneous reaction to the injection of 0.02 cc. of a 1 : 10,000,000 dilution of horse serum. The amount of protein present in this dose corresponds to that in about 3,000 tubercle bacilli in dry material. As the tubercle bacilli are only partially soluble and contain much inert material, a much larger number of tubercle bacilli is equivalent to the minimum amount of horse serum producing a noticeable reaction. The cutaneous reaction, like the anaphylactic shock, is an artificial phenomenon, and it indicates the presence of allergy in the original sense used by Pirquet, namely, that there is a change in the reaction of the tissue as compared with that of the normal tissue. The cutaneous reaction, and especially the necrosis, do not show directly what the reaction is under natural conditions when a few bacteria are located in the tissue.

I cannot agree further with the opinions expressed by Rich, namely, that the allergy itself is without importance for the immunity response. Bacterial allergy does not consist solely in the ability of the tissue to react with the production of acute inflammation in the presence of the antigen. It represents a phase in the development of the immunity process, and it involves a much wider problem than the inflammatory reaction. The experiments described by Rich and his associates were related to the inflammatory reaction caused by allergy and furnished no evidence against the importance of allergy itself. For instance, Rich attributed importance to the observation that desensitization to tuberculin does not destroy the resistance of tuberculous guinea-pigs to a new infection. This observation, in my opinion, does not eliminate the importance of bacterial allergy in the sense in which the term is used in this paper.

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36. (*a*) Rich, A. R.: Arch. Int. Med. **43**:691, 1929. (*b*) Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp. **44**:273, 1929. (*c*) Rich, A. R.; Chesney, A. M., and Turner, T. B.: ibid. **52**:179, 1933. (*d*) Rich, A. R.; Jennings, F. B., and Downing, L. M.: ibid. **53**:172, 1933. (*e*) Rich, A. R., and Brown, H.: Proc. Soc. Exper. Biol. & Med. **27**:695, 1930. (*f*) Rothschild, H.; Friedenwald, J. S., and Bernstein, C.: Bull. Johns Hopkins Hosp. **54**:232, 1934.

Desensitization depresses temporarily certain manifestations of the allergy, but one is not, therefore, justified in concluding that it suppresses the allergic condition itself. The animal after desensitization is not in the condition of a noninfected animal. The specific process, indicated by the inflammatory reaction, persists, and if the desensitizing injections are discontinued the inflammatory reaction reappears in a short time. It is also necessary to distinguish between bacterial allergy and the anaphylactic type of sensitiveness. The treatment used in the experiment with pneumococci and Bacillus avisepticus by Rich, Jennings and Downing [36d] would not, according to my observations, produce bacterial allergy, and no proof is presented that the inflammatory reaction obtained in these animals corresponded to the reaction to tuberculin.

The difference of opinion between Rich and me in the interpretation of the significance of bacterial allergy is probably, as in many scientific discussions, more apparent than real. It is the result of a different conception of allergy. The observations reviewed in this paper argue in favor of a wider and more exactly defined conception of allergy than that used by Rich.

NONSPECIFIC FACTORS IN THE HEALING PROCESS

An infection is usually followed by various nonspecific changes in the infected organism. These are partly local, such as the tissue reaction and the inflammation at the site of the localization of the parasite, and partly general, such as the fever and the alteration in the white cell count. The origin of these nonspecific changes and their effect on the course of the infection are little understood, and in the following pages I shall consider only a few which seem to have a direct bearing on the problems discussed in this paper.

Numerous instances are known which show that certain types of inflammation increase markedly the resistance to various infections. Gay and his associates [37] observed that the inflammatory reaction produced by the injection of an albuminoid substance and lecithin increases the resistance of the peritoneum or the pleura to streptococcic infection. The resistance probably depends on the accumulation of certain types of mononuclear cells. It is remarkable that not only the cavity prepared by the injection of the albuminoid substance and lecithin but the nonprepared cavities also are resistant, and one can observe how the inflammatory cells wander through the tissues to the site of infection. The local immunization of Besredka depends on a process analogous to that described by Gay. Ledingham [38] observed that in the skin of the rabbit

37. Gay, F. P., and Clark, A. R.: Arch. Path. **1**:847, 1926. Gay, F. P.; Clark, A. R., and Linton, R. W.: ibid. **1**:857, 1926.

38. Ledingham, J. C. G.: Brit. J. Exper. Path. **8**:12, 1927.

areas into which india ink or streptococci were previously injected were not susceptible to infection with vaccinia virus, while the adjacent skin into which no injections were made was fully so. According to these observations, certain types of inflammatory reaction exert a strong protective effect against various infections, the increased resistance depending largely on the presence of mononuclear cells. The significance of macrophages both for active and for passive immunity was discussed in a recent article by Gay.[39]

I have observed another effect of the development of the local inflammatory lesion at the site of infection; this consisted of a powerful increase in the specific response if the antigens were absorbed from the lesion.[40]

An experiment with guinea-pigs illustrating this point was described on page 370. The influence of tuberculous lesions on the specific response is just as marked in rabbits. If an appropriate dose of egg white is used in the rabbits in which injections are made into the tuberculous lesions large necrotic cutaneous reactions will result and precipitins will be produced in abundance. In the rabbits which are infected in the same way and given injections of the same dose of egg white subcutaneously and cutaneously or intravenously no sensitiveness of the skin will result and no antibodies will be produced.[25] This effect of the local lesion develops soon after infection;[41] in the testicles of guinea-pigs it was fully developed in twenty-four hours. The specific effect of egg white injected simultaneously with tubercle bacilli or five hours after the injection was not increased. It is of interest that the influence of tuberculous lesions is especially apparent if very small doses of antigens are used. I observed maximal sensitization of the skin and production of precipitin after the injection of 0.1 mg. of egg white in rabbits, and in guinea-pigs even 0.001 mg. sometimes exerted a great influence on the development of sensitiveness of the skin. These doses are nearly equal to those which are present in the lesions in natural infections and are in marked contrast to the doses which are often used for sensitization and especially for the production of antibodies.

So far, this result of the infection has been observed with the tubercle bacillus, smallpox vaccine and certain spontaneous infections of rabbits. Neither Hanks nor I have observed it in inflammatory reactions produced by chemical or mechanical irritation[41] or in infectious foci produced in guinea-pigs with such organisms as the staphylo-

39. Gay, F. P.: J. A. M. A. **97**:1193, 1932.

40. (*a*) Dienes;[25] (*b*) footnote.[3b] (*c*) Hanks.[5a] (*d*) Dienes, L., and Schoenheit, E. W.: J. Immunol. **19**:41, 1930.

41. Dienes and Schoenheit.[40d] Hanks.[5a]

coccus, the pneumococcus and the colon and the typhoid bacillus. These organisms do not produce in guinea-pigs an infectious process comparable to that in natural infections, and they are probably more similar in their effect to chemical irritants.

The result of infection on the production of antibodies was recognized by Lewis and Loomis.[23] It is probable that in all infections, especially in those which are generalized, besides the influence which the lesion exerts on the immunity response, the response of the whole organism is altered, as compared to that of the normal state.[42] There is little information on this problem, and it cannot be further discussed here.

According to the observations just reviewed, in certain infectious diseases a nonspecific mechanism is present in the anatomic lesions which increases the specific effect of antigens absorbed from the lesions. If small doses of antigen are absorbed this mechanism strengthens especially the development of the first phase of the immunity response, the tuberculin type of hypersensitiveness. If the resorption of antigen from the lesion is repeated during a longer period, the production of antibodies is also largely increased. In an earlier section of this paper I described how the tuberculin type of hypersensitiveness quickens and increases the strength of the tissue reaction around the area in which the antigen is deposited, and it was stated that in this reaction mononuclear cells are predominant. These cells are similar in many respects to those observed in the experiments of Gay and the local immunization of Besredka which were thought to be responsible for the prevention of infection. It is evident from the preceding considerations that in certain infectious diseases a complicated response is present, depending partly on the local lesions and partly on the specific immunity response, which is effective in producing quickly and in abundance certain cell types in the areas in which the infectious agent is localized. In direct experiments these cell types were observed to increase greatly the resistance to infection. It is probable that the presence of this complex response is of great importance in the outcome of an infection.

That nonspecific factors at the site of infection are important for the healing process is apparent in tuberculosis. Lurie [43] studied the fate of tubercle bacilli in rabbits after intravenous injection, and he observed that both nonvirulent human and virulent bovine bacilli multiply after injection in all organs in which they are deposited; however, after some time the human bacilli stop multiplying and often are destroyed in all the tissues, while the bovine bacilli are destroyed in the liver and spleen but continue to multiply undisturbed in the kidney and lungs. This is

42. Schultz, M. P., and Swift, H. F.: J. Exper. Med. **60**:323, 1934. Dienes, L.: J. Immunol. **23**:29, 1932.

43. Lurie, M. B.: J. Exper. Med. **45**:155, 1928; **50**:747, 1929; **57**:181, 1933.

confirmed by the observation that macroscopic lesions develop only in these organs. At the time of injection only a few bacteria are deposited in the kidney; the later multiplication, therefore, cannot depend on the heaviness of the original infection. I have made observations [44] on guinea-pigs which in many respects are comparable to those of Lurie. Guinea-pigs were immunized by killed tubercle bacilli or by infection with the RI strain of tubercle bacilli and inoculated later by intravenous injection of virulent tubercle bacilli. This route of infection produces in normal animals massive tuberculosis of the lungs, since the bacteria are mainly deposited there. In many instances the immunity of the lungs was sufficient in the immunized animals to prevent the development of noticeable lesions there, but the spleen usually showed massive involvement. In guinea-pigs the spleen is the organ most sensitive to tuberculous infection, and its resistance cannot be raised to the same degree as that of the lungs.

These examples prove that even in such a disease as tuberculosis, in which the pathologic changes are localized in the connective tissue and are closely similar everywhere in the organism, the healing or the progress of the lesions after the immunity response is developed depends to a large extent on nonspecific factors prevalent in the different organs. In acute infectious diseases no instances are known which show as clearly the influence of the surrounding tissue on the healing of lesions, though the fact that anatomic lesions in generalized infections are regularly localized to a certain tissue presents analogies to it. In smallpox, for instance, the virus is distributed in the whole organism, but anatomic lesions usually develop only in the skin and mucous membranes. When the immunity reaction starts in the inner organs the virus is destroyed without causing visible injury, while in the skin and mucous membranes necrosis sets in and the virus is not killed.

The three sets of observations that were discussed in this section indicate that the nonspecific factors which are effective in the anatomic lesions at the site of infection exert various and powerful influences on the processes which end in the healing of the disease. The nonspecific resistance of the tissues may be considerably increased in the lesions, and the intensity of the specific response of the whole organism may be increased by the influence of local lesions to an otherwise unknown degree. Since the active immunization of the tissues is probably the decisive influence in the healing, the development of the specific response in the lesions themselves and in the surrounding tissues is probably the most important factor in the whole process of healing. The fate of the infection depends to a large extent, apparently, on the nonspecific

44. Unpublished observations.

and specific processes which occur in the anatomic lesions from the first localization of the infectious agent, and the anatomic lesion is not only the most characteristic sign in the different diseases but the most important agent in the physiologic mechanism of the healing.

The contrast between the healing of vaccinia infection in guinea-pigs and that of smallpox in man, the former preceding and the latter following after a considerable time the development of general immunity, indicates also that the healing is not a simple process of immunization but the result of many contributing factors, in which the immunity plays a more or less significant rôle.

SUMMARY

It must be evident to every one that the information concerning the various processes which go on during infectious diseases and end in healing is fragmentary and that probably fundamental parts of these processes are still unknown. The usual explanation of the healing is closely similar to Ehrlich's conception, namely, that the healing is equivalent to the production of appropriate antibodies. The efficiency of circulating antibodies in passive immunity and in the neutralization of toxins is firmly established, as well as their usefulness in the treatment of several diseases. One may also state that most of the knowledge of specific immunity is derived from the study of antibodies. The opinions expressed in this paper do not detract from the importance of antibodies, but it is probable that the circulating antibodies alone do not sufficiently account for the immunity response in infectious diseases. From the brief discussion in this paper a much more complex picture is obtained of the specific and nonspecific processes on which the healing of infectious diseases depends. The nonspecific tissue reaction at the site of infection may considerably increase the resistance, and in certain diseases it exerts a powerful influence on the whole specific response. The first effect of the specific response, often noticeable in seventy-two hours, is a cellular reaction, enhancing the tissue reaction at the sites at which the infectious agent is present. In the whole specific response in many diseases probably the active immunization of the tissue plays the most important rôle, and the diffusion of free antibodies through the tissue is of less importance; even in the simplest case, for instance, in that of immunization with egg white or horse serum, the diffusion of antibodies reproduces only certain phases of the immunity response. The immunity developing in infectious diseases is necessarily a process of active immunization, and apparently all phases of this process are adapted to the defensive reaction and are closely interwoven with nonspecific processes. The anatomic lesions seemingly play a preponderant rôle in the whole defensive process.

It has already been mentioned that the immunity process in every disease presents a complex individual problem, and the general considerations discussed in this paper are not meant to give an interpretation of these processes. My purpose has been only to call attention to certain aspects of the problem which have been brought to light by recent observations and which may be of importance in the further study of this question.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—Anton Gohn, director of the institute of pathologic anatomy in the University of Prague since 1910, has retired at the age of 70.

Charles Nicolle, director of the Pasteur Institute of Tunis and recipient of the Nobel Prize in physiology and medicine in 1928 for his work on typhus fever, died on Feb. 28, 1936, at the age of 69 years.

Milton J. Rosenau, formerly professor of preventive medicine and hygiene in the Harvard University Medical School, who retired about a year ago, has been appointed director of a newly established division of public health in the medical school of the University of North Carolina.

Alvin J. Cox Jr., instructor in pathology in Stanford University, has been assigned an exchange instructorship in pathology in the University of Freiburg, Germany, and Claus Rosenkranz, of the University of Freiburg, is to work for a year in pathology at Stanford University.

Henry W. Cattell, formerly a Philadelphia pathologist and at one time physician to the coroner's office in Philadelphia, has died at the age of 73 years.

Ivan Petrovich Pavlov, the great Russian physiologist, of Leningrad, died on Feb. 27, 1936, at the age of 87 years.

Francis Amory Septennial Prize.—In compliance with the requirements of a gift under the will of the late Francis Amory, of Beverly, Mass., the American Academy of Arts and Sciences announces the offer of a septennial prize for outstanding work with reference to the alleviation or cure of diseases affecting the human genital organs, to be known as the Francis Amory Septennial Prize. The gift provides a fund the income of which may be awarded for conspicuously meritorious contributions to the field of knowledge "during the said septennial period next preceding any award thereof, through experiment, study or otherwise . . . in the diseases of the human sexual generative organs in general." The prize may be awarded to any person or persons for work of "extraordinary or exceptional merit" in this field.

In case there is work of a quality to warrant it, the first award will be made in 1940. The total amount of the award will exceed $10,000 and may be given in one or more awards. It rests solely within the discretion of the Academy whether an award shall be made at the end of any given seven-year period and also whether on any occasion the prize shall be awarded to more than a single person.

While there will be no formal nominations, and no formal essays or treatises will be required, suggestions are invited. These should be made to the Amory Fund Committee, care of the American Academy of Arts and Sciences, 28 Newbury Street, Boston.

Obituaries

FREDERICK ROBERT ZEIT

1864-1935

Dr. Frederick Robert Zeit, born in Switzerland in 1864, was descended from Huguenot ancestors who migrated from France after the St. Bartholomew massacre in 1572. He received his preliminary education at the Gymnasium of Elberfeld. As a youth he came to the United States with his family and became one of the most loyal of American citizens. His Americanism was of the type that characterized men like Carl Schurz. In 1887 Dr. Zeit graduated in medicine from the Western Reserve University. After practicing in Wisconsin for ten years he came to Chicago and for three years was associated with Edwin Klebs, one of the discoverers of the diphtheria bacillus. In 1898 he became a member of the faculty of the Northwestern University Medical School and gave thirty-seven years of faithful service to that institution. From 1902 to 1923 he was head of the department of pathology. In the latter year, at his own request, he was relieved of the burden of administrative duties, but continued to give his deservedly famous course on tumors each year until the spring of 1935. He died on Dec. 5, 1935.

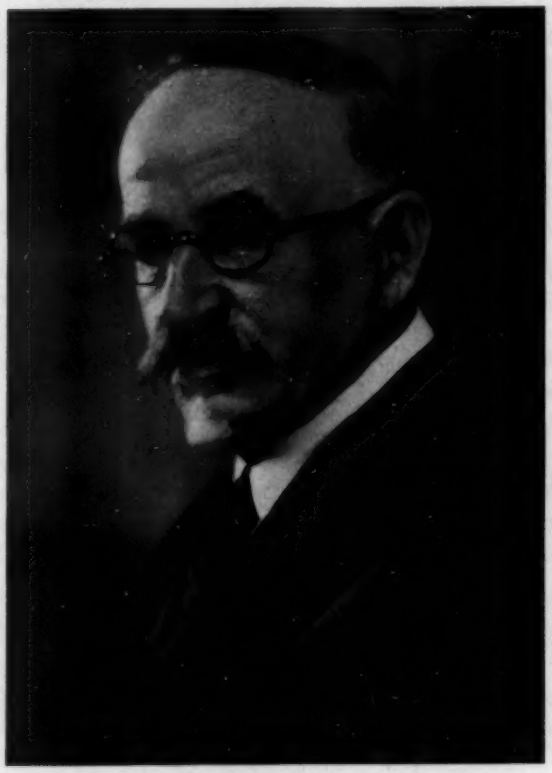
He enjoyed teaching and loved students. From his own experience and observations and from his wide knowledge of medical literature, especially German, he formulated in his own mind definite opinions on the various problems of pathology. He possessed the rare faculty of presenting those principles which he believed to have been firmly established with a lucidity conducive to clear understanding. This made him popular with students; his almost fatherly interest in them won him their deep and sincere affection. They respected the teacher; they loved the man.

From 1900 to 1919 Dr. Zeit was also professor of pathology and bacteriology at the Post-Graduate Medical School of Chicago. Here he came in contact with physicians who had not had an opportunity as students to learn laboratory methods of diagnosis. He thus added much to improvement of the practice of scientific medicine by the general practitioner.

Soon after coming to Chicago he became a member of the Chicago Pathological Society and for many years attended its meetings. His presidential address in 1904 on "The Present Status of Pathology" fore-

told many of the lines of development which have characterized the science of pathology during the past three decades.

The greater part of Dr. Zeit's time and energy was devoted to teaching in the two institutions with which he was connected, but he found time to make several contributions to medical literature. The earliest of these was a very careful study entitled "The Pathology and Bacteriology of Uretero-Intestinal Anastomosis" (New York M. J. **73**: 756,



FREDERICK ROBERT ZEIT
1864-1935

1901), based on an examination of 141 dogs on which this operation had been done by Reuben Peterson and the late Franklin Martin. Dr. Zeit was one of the earliest investigators in Chicago to demonstrate Spirochaeta pallida in syphilitic lesions. Some of the Levaditi preparations which he made more than twenty-five years ago are still used in teaching medical students at the Northwestern University Medical School. One of Dr. Zeit's graduate students, P. D. Guiterrez, was one of the first, if not the first, to succeed in producing experimental blasto-

mycosis. Unfortunately, this well illustrated paper was published in a small journal of limited circulation (*Quart. Bull. Northwestern University Medical School* **12:72**, 1910) and is therefore little known. Although Dr. Zeit's chief interest was in tumors and although he had a huge collection of slides from all manner of neoplasms, he published only three papers on this subject. The most important of these was his comprehensive study entitled "Morphologic and Histogenetic Characteristics of Endothelial Tumors" (*J. A. M. A.* **46:** 567 [Feb. 24] 1906).

Dr. Zeit served as expert witness in many important medicolegal cases. Like other honest pathologists, he often lamented the existence of a "system" which "tends to make partisans, in spite of the best intentions on the part of the scientific specialist." He cooperated with E. O. Jordan, H. L. Russell and others in the fundamental studies on the longevity of the typhoid bacillus in water, studies which had much to do with the building of Chicago's drainage canal.

Dr. Zeit had many interests outside his profession, especially electricity and navigation. His 45 foot boat "The Wanderer" was for many years a familiar craft in most of the harbors of Lake Michigan.

He founded and built up the pathological museum of the Northwestern University Medical School. In 1926 this fine collection of teaching material was officially named "The Frederick Robert Zeit Museum of Pathology," and in 1927 it was formally dedicated with the unveiling of a bronze plaque over its entrance. This museum is essentially "a library composed, not of books, but of the things themselves about which books are written." It is a fitting memorial to a great physician, a true scientist and an inspiring teacher.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

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Experimental Pathology and Pathologic Physiology

Experimental Gastric Erosions Following Hypothalamic Lesions in Monkeys. E. C. Hoff and D. Sheehan, Am. J. Path. **11**:789, 1935.

Of sixteen monkeys subjected to hypothalamic injury five showed multiple hemorrhagic erosions in the mucosa of the body of the stomach. The animals showed striking individual variations in the general postoperative condition. Those with gastro-intestinal lesions showed a disinclination to eat, their condition became progressively worse, and in three experiments death supervened within from twenty-four to forty-eight hours. In all of the cases the erosions were confined to the stomach, none occurring in the duodenum. The erosions were multiple and hemorrhagic, entirely confined to the mucosa, and some showed a punched-out appearance. In three of the five experiments in which gastric erosions were present the stomachs showed considerable dilatation and atony, suggestive but not conclusive evidence of sympathetic activity. Histologic examination of the hypothalamic injuries revealed that in all the animals showing gastric erosions at autopsy the lesions were small and confined to the tuberal nuclei. In only one of the five was the track of the injury hemorrhagic. Positive evidence is therefore advanced to show that histologically verified lesions, confined to the tuberal nuclei and leaving all other hypothalamic nuclei intact, may lead to hematemesis and multiple mucosal erosions in the body of the stomach. In a control series of over fifty monkeys subjected to many and varied types of nonhypothalamic cerebral lesions careful postmortem examination of the gastro-intestinal tracts revealed only one animal with gastric or duodenal ulceration, and this animal had been subjected to a bilateral motor and premotor extirpation five months prior to being put to death and to transections of the spinal cord at the sixth thoracic and third cervical levels five weeks and twelve days, respectively, before autopsy. The consistently negative observations in the control experiments appear to lend greater significance to the association of gastro-intestinal lesions with injury of the hypothalamus or interruption of descending autonomic pathways.

From the Authors' Summary.

The Hypophysis Cerebri of the Finback and Sperm Whale. E. M. K. Geiling, Bull. Johns Hopkins Hosp. **57**:123, 1935.

The pituitary gland of the finback (Balaenoptera physalus) and of the sperm (Physeter megalocephalus) whale is made up of a large flattened anterior lobe and a smaller posterior lobe, separated by a septum. There is no discernible pars intermedia. Extracts of the powder of the acetone-desiccated posterior lobe of both species possess pressor, antidiuretic and oxytocic activity. The pressor and antidiuretic principles are present in the same concentrations as in the standard powder (beef), but the oxytocic principle is present in a much smaller concentration; in that from the finback whale there is about 40 per cent, and in that from the sperm whale only 8 per cent, of the activity found in an equal weight of the standard powder. The melanophore principle is not in the posterior but in the anterior lobe. It is concluded that the pressor and oxytocic components are elaborated in the neural lobe and are not derived from the pars intermedia. The anterior lobe has the gonadotropic (follicle-ripening and luteinizing) hormones (the luteinizing principle in relatively smaller concentration, however, than in the sheep's anterior

lobe), also the thyrotropic and adrenotropic principles (Lawrence). The prolactin content of the anterior lobe is very low; a good yield of follicle-stimulating hormone is to be obtained, and the presence of the thyrotropic factor is demonstrable (Riddle and Bates). FROM THE AUTHOR'S SUMMARY.

RESISTANCE OF VITAMIN B_1 AND B_2 DEFICIENT RATS TO HERPES VIRUS. E. V. COWDRY, A. M. LUCAS and C. F. NEFF, J. Infect. Dis. **57**:174, 1935.

Rats deficient either in vitamin B_1 or B_2 show slightly more deaths when herpes virus is injected into their brains than do normal rats treated in the same way, but the evidence is not sufficient to show that these deficiencies actually reduce their resistance to herpes. FROM THE AUTHORS' SUMMARY.

Pathologic Anatomy

FULMINATING HEMORRHAGIC ENCEPHALITIS. A. LEVINSON and O. SAPHIR, Am. J. M. Sc. **190**:42, 1935.

Fulminating hemorrhagic encephalitis is characterized by sudden onset, great respiratory difficulty, coma and rapid death. The course of the disease is very short, and death may sometimes be sudden. The cerebrospinal fluid may be hemorrhagic but is usually clear. It may have an increase in cells or may show no changes. The greater the meningeal involvement, the more pronounced are the cerebrospinal fluid changes. Histologically, the brain reveals a predominance of a hemorrhagic exudate in addition to perivascularly arranged lymphocytes and neutrophils. In one instance, fulminating hemorrhagic encephalitis was found superimposed on old encephalitis. In children, a generalized enlargement of the lymph glands is usually present. Sudden death due to fulminating hemorrhagic encephalitis may be regarded as "sudden death from natural causes," in Kolisko's definition of the term. FROM THE AUTHORS' SUMMARY.

STUDIES ON THE RELATION BETWEEN MICROGLIA, HISTIOCYTES AND MONOCYTES. H. S. DUNNING and J. FURTH, Am. J. Path. **11**:895, 1935.

Microglia and histiocytes are morphologically and functionally identical and constitute a single cell type. Monocytes may transform into cells indistinguishable from this type. FROM THE AUTHORS' CONCLUSIONS.

PRIMARY AMYLOIDOSIS. H. A. REIMANN, R. F. KOUCKY and C. M. EKLUND, Am. J. Path. **11**:977, 1935.

Primary amyloidosis is characterized by absence of any preceding disease, by lack of involvement of the organs and tissues usually affected in the secondary form, by involvement of the mesodermal tissue, cardiovascular system, gastrointestinal tract, smooth and striated muscle and lymph nodes, by variation in staining reactions and by a tendency toward nodular deposits. A case is described of amyloidosis of the tongue, heart, lung, esophagus and pelvic organs in a woman 41 years old.

CEREBELLAR PARENCHYMATOUS CORTICAL ATROPHY (SUBACUTE CEREBELLAR ENCEPHALITIS). H. L. PARKER and J. W. KERNOHAN, Arch. Neurol. & Psychiat. **33**:959, 1935.

In a man, aged 40, with signs of cerebellar disease, who died within twelve months after the onset, Parker and Kernohan found a small, atrophied cerebellum. The Purkinje cells were for the most part destroyed, leaving so-called empty baskets; Bergmann's cells were increased, the granular layer was atrophied and the amount of microglia cells and astrocytes in the molecular layer was increased.

Some blood vessels were infiltrated, and there was accumulation of glial cells along the dendrites of former Purkinje cells, resulting in bushlike formations. In general, the picture was one of subacute cerebellar encephalitis with conspicuous involvement of the Purkinje cells and preservation of the fiber tracts to and from the cerebellum. The vermis was less involved than the hemispheres. The authors suggest the possibility of a specific infection analogous to louping ill, a disease observed in sheep in the border counties between England and Scotland, which involves mainly the Purkinje cells.

GEORGE B. HASSIN.

ABERRANT PANCREATIC TISSUE IN THE GASTRO-INTESTINAL TRACT. C. D. BRANCH and R. E. GROSS, Arch. Surg. **31**:200, 1935.

Approximately two hundred cases in which aberrant pancreatic tissue was found have been recorded in the literature. In the majority of these the tissue occurred in the gastro-intestinal tract. This report adds twenty-four other cases in which aberrant pancreatic tissue was found in various locations in the wall of the alimentary canal. The distribution was as follows: in the stomach or pylorus, three instances; in the duodenum, two (in one, in a duodenal diverticulum); in the jejunum, four; in the ileum, one; and in a Meckel diverticulum, six. These structures contained ductal and acinar elements which histologically resembled that of normal pancreatic tissue. In sections of fifteen of the specimens there were no islets of Langerhans, but in those of the other nine there were typical islets. The patients in whom the anomalous tissue was found were aged from 8 days to 82 years. The cases occurred in equal numbers in males and females.

The presence of this aberrant pancreatic tissue in the gastro-intestinal tract probably represents a congenital anomaly in most, if not in all, instances. In four of the twenty-four cases the tissue had pathologic importance: In one the nodule caused pyloric obstruction, and in the other three it was the site of ulceration in the stomach or duodenum. Such a nodule in the wall of the gastro-intestinal tract has been mistaken for carcinoma. The gross appearance of the tissue should indicate that it is pancreatic and should obviate the danger of unnecessary removal when it is not the cause of intestinal obstruction or the site of an important pathologic lesion.

FROM THE AUTHORS' SUMMARY.

Pathologic Chemistry and Physics

THE PLASMA-CELL PARTITION OF BLOOD LEAD IN CLINICAL LEAD POISONING. H. BLUMBERG and T. F. M. SCOTT, Bull. Johns Hopkins Hosp. **56**:311, 1935.

The plasma cell partition of blood lead was studied in eighteen cases of clinical lead poisoning by spectrographic analyses of the separated fractions from oxalated, citrated and heparinized samples, as well as by analyses of serum and clot. The results showed that by far the greater part (usually about 90 per cent) of the lead appeared to be carried by the cells or clot. Analysis of control bloods, including a hemophilic sample, indicated that the cell fraction contained at least half, and usually much more, of the trace of nonpathologic blood lead. Washing the cells twice with isotonic saline solution failed to remove appreciable quantities of the lead, thus demonstrating that the lead and the red cells were in comparatively firm combination.

FROM THE AUTHORS' SUMMARY.

A PARADOXICAL RELATION BETWEEN ZETA POTENTIAL AND SUSPENSION STABILITY IN S AND R VARIANTS OF INTESTINAL BACTERIA. E. W. JOFFE and S. MUDD, J. Gen. Physiol. **18**:599, 1935.

The relation between the electrokinetic potential and the suspension stability of four strains of nonflagellate intestinal bacteria has been studied. The smooth forms have zeta potentials which approximate zero over a wide range of p_H and salt concentration yet form nevertheless stable suspensions. The rough variants

have zeta potentials which vary with p_H and electrolyte concentration in the familiar way. The rough forms have values of zeta potential critical for their suspension stability.

FROM THE AUTHORS' SUMMARY.

A PHYSICAL-CHEMICAL DIFFERENCE IN ANTIBODIES AGAINST THE S AND R VARIANTS OF A SINGLE BACTERIAL STRAIN. E. W. JOFFE, J. Gen. Physiol. **18**:615, 1935.

Antibodies to the rough and smooth variants of Bacterium typhosum O 901, when studied as deposits on the maximally sensitized bacterial surfaces, differed significantly in iso-electric points and in zeta potentials. With increasing time of immunization of rabbits the iso-electric points of sensitizing antibody deposits shifted progressively to the alkaline side. Agglutination titers did not change concurrently. Thus two serums may have the same agglutination titers but may form, on the homologous bacterial strains, sensitizing surface deposits whose iso-electric points differ by from 0.5 to 0.8 p_H unit. In rabbits immunized with single cell strains of O 901 S there gradually developed antibodies for O 901 R and vice versa.

FROM THE AUTHOR'S CONCLUSIONS.

THE SILICON DIOXIDE CONTENT OF THE LUNGS OF INFANTS AND OF PLACENTAL TISSUE. WILLIAM D. MCNALLY and W. L. BERGMAN, J. Indust. Hyg. **17**:171, 1935.

Silicon dioxide is a normal constituent of all tissues of the human body. It is present in the fetal lung, in the placenta, in the umbilical cord and in the placental blood. The presence of fluorides in the blood accounts for the formation of fibrous tissue from inhaled silica and strengthens the opinion previously rendered that silicosis is caused by chemical rather than by traumatic action.

FROM THE AUTHORS' SUMMARY.

Microbiology and Parasitology

MICROSCOPICAL EVIDENCE OF THE EXISTENCE OF SAPROPHYTIC VIRUSES. J. E. BARNARD, Brit. J. Exper. Path. **16**:129, 1935.

Refined microscopic examination of the deposits which sometimes occur in culture medium containing horse or rabbit serum reveals minute bodies which, in size and constancy of size, in shape and in constancy and regularity of shape, and also in general optical properties, are in no way different from viruses acknowledged to be pathogenic. The bodies increase in numbers, and photographs show them in process of fission. They have been cultivated to the fourth subculture. It is concluded that these bodies have the nature of a virus. This demonstration that viruses occur which are saprophytic in habit and which multiply in the absence of tissue cells answers in itself certain theoretical objections to the view that viruses are living organisms.

FROM THE AUTHOR'S SUMMARY.

HISTOPATHOLOGY OF THE EXPERIMENTAL B VIRUS DISEASE IN RHESUS MONKEYS AND RABBITS. A. SABIN and E. W. HURST, Brit. J. Exper. Path. **16**:133, 1935.

In the rhesus monkey the B virus produces lesions characterized by the formation of acidophilic intranuclear inclusions and later by cellular necrosis and inflammatory reaction. Lesions can probably develop in any tissue or organ but under the experimental conditions considered here were found in the skin, liver, spleen, adrenals, ovary, lymph nodes and nervous system. Intracerebral inoculation is rapidly fatal, usually with more marked involvement of the membranes than of the nervous parenchyma; after peripheral inoculation there is relatively little

tendency toward invasion of the central nervous system. The disease in the rabbit is similar to that in the monkey save that adhesive peritonitis does not follow intraperitoneal inoculation and that peripheral inoculation leads constantly to ascending infection of the nerve axis. The points of distinction between B virus disease, pseudorabies and herpes are indicated, and the theoretical significance of the lesions in the rabbit's nervous system is discussed. FROM THE AUTHORS' SUMMARY.

SUSPENSIONS OF ELEMENTARY BODIES FROM VACCINIA FILTRATES. G. H. EAGLES, Brit. J. Exper. Path. **16**:181, 1935.

A method has been described whereby large quantities of the virus of vaccinia, consisting of suspensions of elementary bodies, may be obtained. These suspensions are of high potency and are a valuable addition to the sources of bacteriologically sterile vaccine virus and may possibly find a place in the practice of vaccination. They produce typical vaccinial reactions in animals on intradermal inoculation and on scarification. These reactions are followed by immunity to subsequent vaccination.

FROM THE AUTHOR'S SUMMARY.

THE CULTIVATION OF VACCINIA VIRUS. G. H. EAGLES, Brit. J. Exper. Path. **16**:188, 1935.

The behavior of the virus of vaccinia in a medium apparently free from whole living cells has been further investigated. A number of series of subcultures are presented in detail. The difficulties encountered in previous experiments were again experienced. These are shown by the poor survival of the virus in large numbers of individual flasks and the inability to secure either growth or survival of the virus in a number of subcultures. Multiplication of the virus apparently took place in two of the series of subcultures. Possible sources of error in technic and interpretation have been carefully considered and investigated. But no source of error has been identified which suggests that subcultures successful as judged by titrations may not be interpreted as evidence of growth in a cell-free medium.

FROM THE AUTHOR'S SUMMARY.

THE MORPHOLOGY AND LIFE CYCLES OF THE ORGANISM OF *Pleuropneumonia Contagiosa Boum* (*Borrelomyces Peripneumoniæ* NOV. GEN.). A. W. TURNER, J. Path. & Bact. **41**:1, 1935.

The life cycles and morphologic aspects of the causal organism of pleuropneumonia contagiosa bovum have been studied in the living state by dark-ground observation of macrocultures and microcultures in a new fluid medium, V.F.-O.S. broth. The microbe is no filtrable virus in the strict sense but typically and constantly forms a relatively enormous branching mycelium, filaments of which may reach a length of at least 190 microns; certain unbranched filaments have reached 140 microns. It owes its filtrability to the constant and early production of filter-passing forms (conidioids). It possesses at least five different methods of reproduction, for which the term "genethodes" is proposed; these are: (1) by endomycelial fragmentation into coccoidal particles (proconidioids) that become conidioids; (2) by formation in the mycelium of discules that develop into asterodiscules and shed exoconidioids, which become conidioids; (3) by budding from spherules; (4) by formation of oval sporelike bodies from long filaments that arise from masses of clublike bodies, and (5) by pinching off variously shaped forms from cylindric rod-shaped bodies that arise directly from conidioids. There is no evidence for any form of sexual conjugation. Its polygenethodism, extreme pleomorphism and protean faculty of rapidly changing its shape prevent its satisfactory inclusion in any existing order of Schizomycetes. A new order, Borrelomycetales, to include it and the closely related organism of agalactia is proposed. The suggested term for the new order is "Borrelomyces (nov. gen.) peripneumoniæ."

FROM THE AUTHOR'S SUMMARY.

PLEOMORPHISM OF BACT. TULARENSE. H. OHARA, T. KOBAYASHI and J. KUDO, Tohoku J. Exper. Med. **25**:520, 1935.

Old and attenuated cultures of Bacterium tularense consist mostly of coccoid forms with a few short rods which show little or no motility. Fresh cultures, especially after passage through susceptible animals, contain motile coccoid forms and rods of various sizes. The rods are markedly pleomorphic and do not stain uniformly. A polar flagellum can be demonstrated in smears of cultures grown on egg yolk for twenty-four hours and stained according to the method of the Saizawa and Sugawara. The more virulent the culture is the greater the motility and the pleomorphism. The motility is greater than that of the typhoid bacillus.

S. B. PESSIN.

Immunology

THE SHWARTZMAN PHENOMENON. F. PLAUT, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:490, 1934.

An intravenous injection of an antigen (for instance, horse serum, sheep red cells, cultures of Spirochaeta pallida) followed thirty minutes later by an injection of the specific antibody into a rabbit which has previously received a preparatory cutaneous injection of a colon filtrate is known to produce the Shwartzman phenomenon. Plaut tested the action of haptens with their corresponding antibodies. Alcoholic extracts of cultures of Spirochaeta pallida produced the phenomenon, but brain hapten did not produce it. An attempt to use the Wassermann antigen and syphilitic serum gave negative results with rabbit serum. Fresh human serums, syphilitic as well as normal, gave uniformly positive but nonspecific results. The hemorrhagic lesions were not limited to the prepared area of the skin and occurred equally frequently in nonprepared rabbits.

I. DAVIDSOHN.

THE CONSTANCY OF THE ANTIGENIC CHARACTER OF BACTERIOPHAGES. KURT MEYER and T. TASLAKOWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:512, 1934.

The antigenic properties of several Bacillus coli phages were not changed by prolonged cultivation with different strains of B. coli. This indicates, according to Meyer and Taslakowa, the independence of the phages from the bacteria on which they act. It supports the view of d'Herelle that bacteriophages are independent living beings, and not merely products of bacterial metabolism.

I. DAVIDSOHN.

IMMUNITY AND CHEMOTHERAPY IN NEW-BORN AND ADULT ANIMALS. H. KROÓ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:1, 1934.

The infection with Spirochaeta gallinarum differs in chickens and in chicks in many ways. Chickens get over the disease in from three to five days, while in chicks the disease lasts from sixteen to twenty-one days. Chickens can be successfully vaccinated with killed spirochetes, while chicks are not protected. Arsphenamine readily sterilizes adult chickens, and permanent immunity results. In chicks the administration of this drug is followed by a short period during which spirochetes are absent, but they reappear soon and have been shown to be immunologically identical with the original infecting strain. Contrary to what is observed of adult chickens, chicks receiving injections of arsphenamine do not reveal any development of spirocheticidal properties in the serum, yet after treatment with arsphenamine they become resistant to further infections. From this it appears that the presence of spirocheticidal properties and resistance to the disease caused by the spirochetes are not necessarily dependent on each other.

I. DAVIDSOHN.

THE RETICULO-ENDOTHELIAL SYSTEM IN THE TREATMENT OF MALARIA. I. L. KRITSCHEVSKI and L. W. DEMIDOVA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:14, 1934.

In birds (Acanthis linaria) infected with Plasmodium praecox a blockade of the reticulo-endothelial system with trypan blue impaired greatly the effect of various chemotherapeutic antimalarial agents. The intact condition of the reticulo-endothelial system is necessary for the effectiveness of chemotherapeutic agents.

I. DAVIDSOHN.

THE BEHAVIOR OF LAKED BLOOD IN COMPLEMENT FIXATION. T. LINK, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:35, 1934.

Link confirmed the finding by Brunius (abstr., ARCH. PATH. **14**:421, 1932) that boiled solutions of red cells are unable to fix complement, while alcoholic extracts of such boiled solutions regain the ability to fix complement. Link found also that the heated solutions possess the ability to absorb antibodies from immune serums. In the special case of complement fixation the inhibiting effect on immune serums proved to be, to some extent, a nonspecific reaction, for heterologous bloods brought about a similar inhibition.

I. DAVIDSOHN.

BACTERIOPHAGE AND PHAGOCYTOSIS OF BACTERIA. F. HODER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:46, 1934.

When staphylococci, typhoid, dysentery and colon bacilli were acted on by their specific phages strains appeared which were more readily taken up by human leukocytes than were the untreated bacteria. The behavior toward the leukocytes of the guinea-pig was not changed. No relation was noted between the development of resistance to the phage, or its absence, and the decrease of resistance to phagocytosis. The result indicates that lysis is merely one of the manifestations of the action of phages on bacteria.

I. DAVIDSOHN.

THE FORMATION OF AGGLUTININS IN FISH. O. NYBELIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:74, 1934.

Inoculation of Vibrio anguillarum and Pseudomonas fluorescens into eels, tenches, perches and eel-pouts stimulated the production of powerful and specific agglutinins. A single injection was sufficient. In fishes kept at room temperature the antibody response was very much better than in those kept at lower temperatures.

I. DAVIDSOHN.

THE HUMAN ANTI-O ISO-AGGLUTININS. J. MORZYCKI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:80, 1934.

Morzycki found anti-O iso-agglutinins in 4 of 1,115 human serums. Three of these four serums acted only at icebox temperature; the fourth, from a person with blood of group A agglutinated O red cells even at incubator temperature. Absorption at different temperatures permitted the separation of anti-B from anti-O agglutinins. The red blood cells of the person who had the anti-O iso-agglutinins in the serum were unable to absorb the anti-O hetero-agglutinins of a normal ox serum, while all other human red cells were able to do it. On the other hand, the red cells of the same person had a very high titer of iso-agglutinogen (from eight to sixteen times that of ten other samples of A blood). The O property may be interpreted as a species-specific quality which is present in varying amounts in almost all persons. Its absence in the red cells permits the appearance of the anti-O agglutinins in the serum.

I. DAVIDSOHN.

THE THERAPEUTIC VALUE OF IMMUNE SERUMS FOR WEIL'S DISEASE AND THE TITERS OF THEIR ANTIBODIES. E. ZIMMERMANN and E. ARJONA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **84**:111, 1934.

The therapeutic efficiency of human convalescent serum and of immune serum from rabbits inoculated with spirochetes can be estimated by means of the protection experiment in guinea-pigs. Zimmerman and Arjona found that the titer of agglutinin and that of lysin of a serum are parallel to its therapeutic efficiency. Rabb's immune serums were as effective in protecting guinea-pigs as human serums. To reproduce a condition similar to the disease in man the infection was accomplished by instilling the spirochetes into the conjunctival sac of the guinea-pigs. The duration of the disease was prolonged to ten days instead of four days following intraperitoneal inoculation. A titer of agglutinins of not less than 1:20,000 is considered essential for therapeutic efficiency of the serum.

I. DAVIDSOHN.

DEMONSTRATION OF AN IMMUNE AGGLUTININ AND A NEW BLOOD PROPERTY CORRESPONDING THERETO. P. H. ANDRESEN, Ugesk. f. læger **96**:1159, 1934.

The new immune agglutinin was found in the serum of a rabbit which had been immunized with O M blood. This rabbit's serum contained, in addition to the human species agglutinin, a strong anti-M agglutinin and an anti-N agglutinin. When the serum was properly absorbed a third specific agglutinin was demonstrable for a property X present in 94 per cent of human bloods. This new property is unrelated to any of the already known agglutinogens O, A, B, M and N.

A. S. WIENER.

Tumors

POLAR SPONGIOBLASTOMA OF THE PONS. COBB PILCHER, Arch. Neurol. & Psychiat. **32**:1210, 1934.

Polar spongioblastoma usually occurs in the pons, the medulla and the region of the optic chiasm and consists mainly of unipolar and bipolar spongioblasts. It is a slowly growing tumor, the polarized spongioblasts tending to invade the interspaces of the glial bundles and causing great enlargement of the organ in which they grow. In some instances polar spongioblastoma contains mainly polarized spongioblasts (pure types); in others it consists, in addition, of either spongioblasts, then resembling multiform spongioblastoma (primitive type), or of more mature cell bodies—astrocytes, then resembling astrocytoma (mature type). The primitive and mature types are, according to Pilcher, transitional forms between the pure type and the multiform spongioblastoma on one hand and the astrocytoma on the other. Clinically they cannot be differentiated, but the primitive type runs a more rapid course. Of the eleven tumors studied, three were of the pure type, according to Pilcher, four of the primitive and four of the mature type.

GEORGE B. HASSIN.

INTRAMEDULLARY TUMORS OF THE BRAIN STEM. CLARENCE C. HARE and ABNER WOLF, Arch. Neurol. & Psychiat. **32**:1230, 1934.

Hare and Wolf studied seven cases of glioma of the brain stem. The tumor for the most part involved the pons whence it evidently extended to the medulla and upper part of the spinal cord or to the thalamus and hypothalamus. All the patients were children—six were younger than 10 years; one was aged 14. The types of glioma were: unipolar spongioblastoma (one case), fibrillary astrocytoma (three cases) and multiform glioblastoma (three cases). All had been operated on, with fatal results shortly after operation. Operation should not be undertaken when a correct diagnosis of glioma of the brain stem has been made.

GEORGE B. HASSIN.

CRANIAL AND CERVICAL CHORDOMA. A. W. ADSON, J. W. KERNOHAN and H. W. WOLTMAN, Arch. Neurol. & Psychiat. **33**:247, 1935.

Of three cases of chordoma, one was in a woman aged 29. It arose from the body of the sphenoid bone and extended "into the middle fossa on the left." It was encapsulated and contained a gelatinous semisolid substance. In the second case, that of a boy aged 8, the tumor originated in the base of the occipital bone—the spheno-occipital synchondrosis. In a third case, that of a woman aged 40, the tumor was in the vicinity of the second cervical vertebra and caused erosions of the transverse processes of the second and third cervical vertebrae and of parts of the laminae of the atlas, axis and third cervical vertebra. In all three cases the tumor resembled embryonic notochord, and microscopic examination revealed physaliphores with a vacuolated protoplasm and a vacuolated nucleus. Many vacuoles contained mucus, and the contents of some gave a positive reaction with Best's staining method for glycogen. However, the authors are not certain whether it was glycogen or some kindred substance, as the tissues were fixed in a solution of formaldehyde. The solution contains water, in which glycogen is soluble, and for this reason the sections could not be properly fixed, cut and stained.

G. B. HASSIN.

SACROCOCCYGEAL CHORDOMA. E. M. FLETCHER, H. W. WOLTMAN and A. W. ADSON, Arch. Neurol. & Psychiat. **33**:283, 1935.

Next to the spheno-occipital, the sacrococcygeal region is the common seat of chordoma, which develops there from the rests of the notochord. The authors report ten cases, some illustrated. The structure of the sacrococcygeal chordoma is similar to that of the intracranial and can easily be diagnosed from the presence of physaliphores. The majority of the cells contain vacuoles filled with mucin; the nuclei are vesicular like the cytoplasm and are often misplaced. The tumor cells occasionally present a lobular arrangement. The tumor is a destructive, soft, gelatinous mass, encapsulated, situated anterior to the sacral bone, which it invades, and it may protrude through the sacral foramina, causing pain along the sciatic nerve.

G. B. HASSIN.

THE ARON REACTION FOR CANCER. P. DESAIVE and L. COHEUR, Arch. internat. de méd. expér. **9**:391, 1935.

The Aron reaction, which is the change in the adrenal cortex of a rabbit on injection of an extract of urine from a patient with cancer, is not a reliable index of cancer.

ELIZABETH MCBROOM.

CARCINOID OF THE APPENDIX. P. TOPA, E. C. CRACIUN and D. CARAMZULESCU, Arch. d. mal. de l'app. digestif **4**:392, 1934.

Carcinoid of the appendix is a rather rare tumor without invasion of the peritoneum, metastasis or postoperative recurrence. The cells are chromaffin as well as argentaffin. The tumor is frequently associated with chronic appendicitis. The carcinoid occurs also outside the appendix—in the small intestine, stomach, colon, duodenum, jejunum, ileum and papilla of Santorini; it has been observed even in the gallbladder, but here no argentaffin cells have been found. As the carcinoid is becoming more and more recognized the diagnosis of true cancer of the appendix is becoming less frequent.

FRED STENN.

SHOULD THE FIBRO-ADENOMA OF THE MAMMARY GLAND BE CLASSIFIED AS BLASTOMA? A. FRAENKEL, Frankfurt. Ztschr. f. Path. **46**:195, 1933.

Fraenkel studied the anatomic structures of a fibro-adenoma of the breast by means of serial sections and subsequent reconstruction by wax models. The fibro-adenoma consisted of two systems of glandular structures which did not communicate with one another. The individual duct structures were in close relation

to the surrounding normal breast tissue. Because of the fact that the fibro-adenoma consisted of two noncommunicating duct structures Fraenkel does not believe that the lesion is a tumor [neoplasm]. Similarities are pointed out between fibro-adenoma of the breast and so-called hypertrophy of the prostate, which is also not considered to be a true neoplasm. He recommends the term "Mastopathia nodosa" instead of "fibro-adenoma of the breast."

OTTO SAPHIR.

LUTEINIZATION OF THE OVARIES IN A CASE OF BASOPHIL ADENOMA OF THE HYPOPHYSIS. HILDING BERGSTRAND, Virchows Arch. f. path. Anat. **293**:413, 1934.

A woman aged 42 years, with progressive symptoms of about ten years' duration, presented at the end the syndrome which Cushing has described as characteristic of basophil adenoma of the hypophysis. Death was due to pulmonary embolism from venous thrombosis following exploratory laparotomy. Necropsy revealed a basophil adenoma of the hypophysis which had penetrated the capsule of the gland and had invaded the cavernous sinus. Menstruation had persisted. The Aschheim-Zondek reaction of the urine was negative. Chief attention is devoted to the ovaries, which had been removed at the exploratory laparotomy. An ovarian reaction not hitherto described in basophil adenoma was luteinization of unruptured follicles. Such a change, which is similar to that associated with hydatidiform mole and chorio-epithelioma, has been brought about experimentally in immature mice by long continued injection of pituitary hormone. In the ovaries there were present also maturing and hemorrhagic follicles, such as are seen in the experimental animal following less prolonged administration of the gonadotropic hormone of the adeno-hypophysis. The findings support the view that the gonadotropic hormone of the adenohypophysis is formed by the basophil cells. In the case reported the adrenal bodies were enlarged. The findings in the endocrine organs are compared with those in a 29 year old acromegalic woman.

O. T. SCHULTZ.

A CASE OF LIPOBLASTIC SARCOMATOSIS. H. SIEGMUND, Virchows Arch. f. path. Anat. **293**:458, 1934.

Three years before the death of a woman aged 65 years a small subcutaneous lipoma had been removed from the thigh. Shortly thereafter numerous small lobulated nodules made their appearance in the skin. Clinical signs of intrathoracic pressure developed and led to death. Necropsy revealed: a tumor the size of a child's head in the mediastinum; multiple small tumors of the subcutaneous fat, omentum, mesentery, pleura and retroperitoneal tissue; massive tumors of the inguinal region, and replacement of the marrow of the femurs by lobulated adipose tissue. Lubarsch had recently described a case of metastasizing lipoma and had stated that he could find no previous record of a similar case. In Siegmund's case the tumors occurred only where adipose tissue is normally formed. They were expansive, not invasive, and were sharply delimited from the adipose tissue in which they occurred. Histologically they differentiated to typical adipose tissue. Some of them contained hematopoietic tissue, as does embryonic fat. For these reasons Siegmund concludes that the process was not a primary lipoma with metastasis but a neoplastic systemic disease of adipose tissue. He likens the process to lympho-sarcomatosis and neurofibromatosis and proposes for it the name "lipoblastic sarcomatosis."

O. T. SCHULTZ.

GIANT CELL TUMOR OF THE LONG BONES. H. W. HOTZ, Virchows Arch. f. path. Anat. **293**:493, 1934.

The conflicting opinions that have prevailed relative to the nature of giant cell tumor of the long bones are briefly reviewed. Three cases are presented in which biopsy led to a diagnosis of a benign lesion, but the course and later histologic characters were those of a malignant one. Hotz concludes that in general

the giant cell lesions of bone with a fibroblastic, spindle cell stroma are benign. He leaves undecided whether they are to be considered benign neoplasms or reactive granulomas. Undoubtedly malignant giant cell tumors occur. Large areas of these may have the histologic characteristics of the benign lesion. Giant cell granuloma and sarcoma may coexist in the same bone, the benign tissue being invaded by the malignant. Correct interpretation of the individual case depends on careful selection of biopsy material and calls for conference of the clinician, the roentgenologist and the pathologist.

O. T. SCHULTZ.

CARCINOMA OF AN ACCESSORY LIVER. F. PAUL, Virchows Arch. f. path. Anat. **293**:551, 1934.

In the small number of previously reported examples of accessory liver the structure has been small, sometimes microscopic, and has been situated in the omentum, the hepatic ligaments, the gallbladder or the spleen. According to the author, the development of carcinoma in such misplaced hepatic tissue has not previously been recorded. The unusual features were the large size of the accessory liver, its retroperitoneal situation to the left of the vertebral column and the development of carcinoma in it. The mass weighed 3 kilograms as compared with 2,200 Gm. for the liver, which revealed the Laënnec type of cirrhosis. The tissue of the tumor was greenish and gave a direct van den Bergh reaction for bilirubin. Histologically it was composed of tissue with the structure of liver parenchyma. The cells contained bile capillaries with bile thrombi, fat vacuoles and glycogen. The tissue was atypical in places and had given rise to pulmonary metastases.

O. T. SCHULTZ.

A PROTEIN-FREE IMMUNOLOGICALLY ACTIVE SUBSTANCE IN EGG-WHITE. M. G. SEVAG and V. SEASTONE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:464, 1934.

Treatment of egg-white with liquid air and precipitation with chloroform and with alcohol resulted in a fraction which according to different tests was protein-free and acted like a carbohydrate. This substance in quantities of less than 1 mg. caused typical anaphylactic shock in guinea-pigs sensitized with egg-white. On the other hand, guinea-pigs treated with injections of this fraction did not react to reinjections of the same substance but reacted feebly to injections of egg-white. The substance did not react in complement-fixation and precipitation tests with a powerful immune serum against egg-white which was prepared according to the method of Hektoen. It was not precipitated by a 20 per cent solution of sulphosalicylic acid.

I. DAVIDSOHN.

THE FRACTIONS OF THE TUMOR ANTIGENS. E. MORELLI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:521, 1934.

Lehmann-Facius published recently a technic which permitted extraction of a tumor-specific antigen from cancerous tissue (abstr., ARCH. PATH. **19**:266, 1935). That antigen reacted only with cancer antiserums but not with species-specific and group-specific antiserums. Morelli repeated that work and was unable to separate the tumor-specific antigen from the other antigenic substances.

I. DAVIDSOHN.

MULTIPLE MENINGIOMA WITH DIFFUSE MENINGIOMATOSIS. H. F. HARBITZ, Acta path. et microbiol. Scandinav. **12**:24, 1935.

Among the multiple tumors and anomalies in the groups spoken of here a combination of the following formations is of fairly frequent occurrence: pure ectodermal tumors and anomalies (pigmented nevi, adenoma of the hypophysis, adenoma of the cutaneous glands); neuro-ectodermal tumors and anomalies (glioma, gliomatosis and abnormalities in the central nervous system, "degenerations," "sclerosis").

Tumors from cell groups which probably have developed from the neural crest: meningioma (solitary and multiple) and meningiomatosis; neurofibroma (neuroma, acoustic tumors), eventually as part of a general neurofibromatosis of the Recklinghausen type; chromaffin tumors, anomalies in the situation and location of the adrenal glands, hypernephroma.

Mesenchymal tumors and anomalies of development: hemangioma and hemangiomatosis in the central nervous system and retina, the skin (vascular nevi), spleen, liver and kidney; cysts and polycystic abnormalities in the liver, kidneys and pancreas.

These tumors and anomalies present certain comparatively typical combinations, such as multiple meningioma and neurofibroma or multiple neurofibromatosis. Further, one has characteristic syndromes of the Lindau and von Hippel types. But otherwise there occur manifold irregular combinations, as indicated by my small collection of cases and by numerous other works on the subject. When once one comes to know these possible combinations one finds, however, that they are so frequent and constant that they can hardly be merely fortuitous but must be due to a dysontogenesis. Moreover, this often manifests itself by the hereditary and familial occurrence of certain characteristic combinations.

CHARACTERISTICS OF MOUSE EPITHELIAL TUMOR CELLS IN VITRO AND TUMOR STRUCTURES IN VIVO. L. SANTESSON, Acta path. et microbiol. Scandinav., supp. 24, 1935, p. 237.

The general significance of the results described in this monograph are given in the author's conclusion as follows: "Epithelial cell proteolysis is of as fundamental importance in vivo as it is in vitro. This finding, together with the results as to the close connection between the degree of cell proteolysis in vitro and the degree of tumor differentiation in vivo, gives rise to the presumption that in vivo the proteolytic characteristic of epithelial cells is of decisive influence on the organization of tissues and on the infiltrative growth of tumors, inasmuch as progressive loss of the proteolytic abilities of epithelial cells results in progressive loss of the capacity for specific tissue organization in these cells, i. e., results in progressive loss of differentiation of the tissue formed by these cells, as well as in increasing power of infiltrative growth of these cells. The discussion of this presumption from various aspects shows that support for it is to be found in numerous observations and facts derived from my own researches, from results of other investigators and from current opinions."

Medicolegal Pathology

VASOMOTOR DISTURBANCES AS A SEQUEL OF ELECTRICAL SHOCK. PIETRUSKY, Deutsche Ztschr. f. d. ges. gerichtl. Med. **25**:197, 1935.

Pietrusky calls attention to some of the phenomena encountered in a body subjected to currents of high voltage. These include edema, venous distention and paresthesia and blueness of the extremities. The features are the same whether the shock is due to lightning or a current, and the extremities become involved as either the point of entrance or the point of exit for the charge.

GEORGE RUKSTINAT.

SIGNIFICANCE OF ELASTIC FIBERS IN THE PULMONARY ALVEOLI OF NEW-BORN CHILDREN. M. STAEMMLER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **25**:202, 1935.

Orcein and Weigert's stains were used to study the elastic fibers in the lungs of twenty-four children. Of these, six were stillborn, twelve lived as long as a day and six lived from a day to three weeks. The body length of the subjects ranged from 27.5 to more than 50 cm. In all the lungs elastic fibers were found, and their staining held no clew as to whether or not the children had breathed.

The mass of such fibers varied with the general development of the child rather than with the establishment of the act of breathing. There was evidence, however, that there was an acceleration of the tempo of development of such fibers after birth. The postembryonal development of elastic fibers was slower in premature infants than in those born at term.

GEORGE RUKSTINAT.

THE SIGNIFICANCE OF THE ELASTIC SYSTEM OF THE LUNG IN FORENSIC MEDICINE. A. FOERSTER, Deutsche Ztschr. f. d. ges. gerichtl. med. **25**:208, 1935.

Foerster reviews the physical and chemical properties of the elastic fibers in the lung and attempts to employ their resistant qualities in the following way. The homogeneous character of decomposed lungs stained with hematoxylin can be restored to some semblance of structure by the use of elastic tissue stains. Applying this knowledge to the lungs of a new-born infant, he believes that he can tell by the character of the elastic fibers whether the infant breathed or not. The distention of the alveoli stretches the elastic fibers so that they appear as smooth bows, or when they break and retract, as corkscrew-like structures. In the undistended lung such fibers appear wavy. He believes these alterations are especially helpful in distinguishing a lung which has contained air and has subsequently undergone decomposition from a lung which has never contained air.

GEORGE RUKSTINAT.

BLOOD GROUPS AND DETERMINATIONS OF PATERNITY IN HORSES. A. KAEMPFFER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **25**:231, 1935.

With the aid of normal iso-agglutinins, six distinct agglutinogens are demonstrable in horse's blood. These agglutinins are very specific, frequently having a titer of from 32 to 64. Kempffer studied the heredity of the six agglutinogens in 260 matings with 361 colts and found that the agglutinogens are all inherited as simple mendelian dominants. For the agglutinogen-agglutinin pairs A-α and B-β, Landsteiner's rule holds, the agglutinin always being present when the corresponding agglutinogen is absent, but for the other four pairs it does not. Most of the genes are neither allelomorphic nor linked, so that a stallion and a mare both of group AB can produce a colt of group O. The author created artificial cases of questionable paternity involving 128 colts, and in 39 cases (26 per cent) the father was determined correctly. In 2 of 7 actual cases the problem of the paternity was solved. The author holds that the medicolegal application of these tests for determining paternity in horses is safe at the present time.

A. S. WIENER.

Technical

TISSUE DIAGNOSIS DURING OPERATION. C. ALEXANDER HELLWIG, Surg., Gynec. & Obst. **61**:494, 1935.

Terry's supravital technic has been adopted as the most favored routine method of diagnosing tumor during operation. Its reliability equals that of frozen sections. In rapidity, it is not surpassed by any other histologic procedure, and it permits, therefore, constant microscopic control of an operation for tumor without causing any delay to the surgeon. It does not prevent subsequent employment of paraffin or pyroxylin (celloidin) sections, even if the biopsy specimens are of extremely small size. It is noiseless and can be employed in the operating room without elaborate equipment.

FROM THE AUTHOR'S SUMMARY.

TESTS FOR INGUINAL LYMPHOGRANULOMA. E. CRISCUOLO, Prensa méd. argent. **22**: 1917, 1935.

In making the Frei test, Criscuolo uses 1 part of sterile pus from a lymphogranulomatous mass to 10 parts of physiologic solution of sodium chloride and

injects 0.2 cc. of this mixture intracutaneously. Dried pus kept in a vacuum and dissolved in the salt solution just before the test is made will retain its activity for more than one year. Hellerström injects Frei's antigen intravenously, the first dose being 0.1 cc., which is increased by 0.1 cc. if further injections are necessary; a positive result shows itself by chills and fever from eight to ten hours after the injection. This test is said by Criscuolo to be harmless, and the injection may have therapeutic value.

USE OF THE SO-CALLED UNIVERSAL DONOR IN BLOOD TRANSFUSION. E. HESSE, Deutsche Ztschr. f. Chir. **245**:371, 1935.

Hesse says that until recently it was generally asserted that persons in blood group O are universal donors. A number of authors have even suggested that in time of war only blood of group O should be used, so as to make the determination of blood groups unnecessary. Recently there has been an increase in the number of cases in which hemolysis followed the transfusion of blood from a universal donor into a patient with another blood group. Hesse found 46 cases reported in the literature, in 20 of which the hemolysis proved fatal. He emphasizes that the transfusion of large amounts of blood (more than 200 cc.) may lead to "retrogressive" agglutination and hemolysis, particularly if the titer of the donor's serum is too high compared with the erythrocytes of the recipient. Investigations were made on the titers of 104 universal donors. In more than 42 per cent the titer exceeded 1:32 with the erythrocytes of group A, and in more than 32 per cent it exceeded 1:32 with the erythrocytes of group B. Such a titer already involves danger of "retrogressive" agglutination. In 14 cases the titer was 1:128 and in 3 cases 1:256. The transfusion of blood from a universal donor with a titer of 1:16 caused no symptoms. However, in cases in which the titer was high or moderately so, signs of hemolytic shock appeared. In the case of transfusion of blood of the same group, the observations disclosed no deviations from the normal, whereas the transfusion of blood from a universal donor produced considerable increases in the pulse frequency (up to 40 beats). This indicates that the nervous system is extremely sensitive toward discrepancies in the blood groups. The transfusion of blood from universal donors is especially dangerous if the recipient belongs to group A, for 15 to 22 persons with hemolytic shock were of this group. The conclusion is reached that there are no universal donors in the strict sense of the term and that transfusions should be made only within the same blood group. If in case of emergency a universal donor has to be used, not more than 200 cc. should be given, and even then the transfusion is permissible only if the erythrocyte count of the recipient has not gone below 2,000,000 and the titer of the donor's serum with the erythrocytes of the recipient does not exceed 1:16. If it is a question of life and death and only a universal donor is available, the lesser of two evils should be chosen and transfusion tried.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Nov. 14, 1935

MORTON MCCUTCHEON, *President*

MADURA FOOT. JUDSON DALAND.

Madura foot is a granulomatous lesion which may be due to infection by several types of fungi. The specimen shown was secured in 1906. At this time various forms of the disease were fairly common among natives of the Madras Presidency, especially in Madura. The skin of the neck, hands, feet, legs and other parts of the body may be involved by the fungi, and the feet of camels and horses sometimes show a similar disease. The lesion begins as a firm swelling of the part. This progresses with thickening, deformity and sinus formation. Black, yellow, gray or white granules, usually about 1 mm. in diameter and composed of masses of fungus, are discharged from the sinuses. The specimen will become the property of the Pathological Museum of the University of Pennsylvania.

BILATERAL ANEURYSM OF THE COMMON ILIAC ARTERIES. P. A. MCCARTY and ELI SALEEBY.

Aneurysms of the iliac arteries are not so common as are those of the aorta. The present case is of interest because the aneurysms were bilateral. C. S., a white man of 55 years, was admitted to the Philadelphia General Hospital on Sept. 14, 1935, complaining that he had had dull pain in the lumbar region for about four years and dull continuous pain in the left leg for about four weeks. Occasionally he experienced sharp shooting pain in the left leg, also. The feet became cold easily and were sometimes numb. Walking was difficult because of the pain. A large pulsating mass was palpated in the left lower quadrant; its presence was also shown by an x-ray picture which demonstrated, in addition, arteriosclerosis of the aorta near its bifurcation. The Wassermann test of the blood was negative. On Oct. 4, 1935, exploratory laparotomy was done. The aneurysm on the left had ruptured into the retroperitoneum. Death occurred shortly after the operation. At autopsy, the aorta and proximal 3 cm. of the iliac arteries were of normal caliber. Below this level the walls of the iliac arteries were involved by aneurysms which measured about 5 to 7 cm. in diameter. That in the left artery communicated with the mass of blood clot in the retroperitoneum. The intima of both sacs contained calcified atheromas, and in the left sac some of these had ulcerated. Microscopic examination revealed chronic nonsyphilitic arteritis of the wall of the right aneurysm and necrosis of the wall of the left.

RENAL LESION FROM PREVIOUS ATTACKS OF TOXEMIA OF PREGNANCY: REPORT OF A CASE. EDWARD WEISS.

Although the belief is widely held that eclampsia can cause permanent renal damage there is remarkably little pathologic evidence to sustain it. Bell's case 3 in a recent paper on the subject appears unique; at least it enjoys the distinction of being constantly referred to as an isolated example of such a lesion. For this reason the following report of a case seems important.

A white woman aged 27, previously in good health, had had four definite attacks of the toxemia of pregnancy (preeclampsia) in a period of six years. She died

in the last attack following operation. Clinical observations beginning in the third month of her last pregnancy showed no evidence of a chronic renal lesion. Nevertheless, microscopic studies of the kidneys demonstrated chronic glomerulotubular changes. The observations varied from nearly normal to completely hyalinized glomeruli. Most of them were somewhat larger than normal, and in some there was an increased number of nuclei. They were almost bloodless. There were no leukocytic infiltrations and no crescent formations. There were many atrophic and also dilated tubules, with acute changes to be noted in the epithelium of the latter. The arteries showed slight sclerosis.

It seemed likely that these acute and chronic renal lesions were the results, respectively, of the present and past attacks of preeclampsia. While there was a doubtful history of nephritis in childhood there was no clinical evidence to point to such a process, and the microscopic picture did not seem to be that of glomerulonephritis. There was nothing to indicate that the lesions had been due to emboli nor was there sufficient cardiovascular evidence to indicate hypertensive vascular disease as a cause. It appeared, therefore, that a chronic renal lesion, insufficient to impair renal function, had resulted from previous attacks of preeclampsia.

THE ABNORMAL NEPHRON OF CHRONIC HEMORRHAGIC BRIGHT'S DISEASE. JEAN OLIVER.

Dissected specimens of the abnormal nephron of terminal hemorrhagic Bright's disease were presented, illustrating the changes that occur in the renal unit from the glomerulus to the ducts of Bellini. Aglomerular tubules, including the complete aglomerular nephron, were shown, and the changes that occur in the arterial supply of the renal parenchyma as a result of the obliteration of the glomeruli were demonstrated. The importance of obstruction at various points of the nephron, particularly in the distal convolution, and its effect as a factor in the production of alterations in the architecture of the contracted kidney were also described.

Dec. 12, 1935

MORTON MCCUTCHEON, *President*

ANNUAL GROSS LECTURE: THE RELATION OF VIRUSES AND TUMORS. PEYTON ROUS.

The lecturer dealt with the accumulating facts which testify to a causal relationship between viruses and certain tumors. The first facts suggestive of such a relationship were obtained through the study of various transplantable tumors of mesoblastic origin in chickens. These growths have the character of typical malignant neoplasms, yet agents can be separated from their cells that will produce similar growths in other fowls. Much evidence on the nature of the agents has gradually become available. Review of it shows them to be viruses of a highly specific sort, which stimulate the cells to neoplastic activities.

Recently a virus has been discovered which causes cutaneous papillomas in western cottontail rabbits, and these growths have been found to have the immediate attributes of tumors. The relationship between the virus and the host and cells is essentially the same as that described for the viruses associated with chicken tumors. The most actively growing virus-induced papillomas in rabbits become carcinomatous. The lecturer discussed the development and the character of the cancers, and the evidence as to their cause. The implications of the observations and findings as a whole were briefly considered.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 26, 1935

IRVING GRAEF, *Secretary, presiding in the absence of the President,*

WILLIAM C. VON GLAHN, M.D.

ACUTE FATAL HEMORRHAGE FROM TUBERCULOUS GASTRIC ULCERS. KURT E. LANDÉ (by invitation).

The following tuberculous manifestations were found in a 46 year old male Negro: small cavities with some bronchiogenic spread in the upper lobes of both lungs; caseous tuberculosis in the left adrenal gland and the right testicle; caseous and miliary tubercles in the liver, and miliary tubercles in the spleen and both kidneys.

Most striking was the appearance of the lymph ducts in the jejunal mesentery; they were dilated and filled with inspissated yellowish material. They could be traced from the surface of the jejunum to conglomerated masses of enlarged mesenteric lymph nodes. Neither ulcerations in the mucosa of the small or of the large intestines nor tubercles along these dilated lymphatic channels could be found. The dilatation was evidently caused by stasis and back pressure following obstruction of the lymphatic channels within the caseated lymph nodes.

In the stomach six small ulcers scattered between the cardiac and the pyloric end had caused a fatal hemorrhage. These ulcers measured from 1.5 to 4 mm. in diameter. Their walls showed typical miliary tubercles. No other tuberculous involvement of the stomach or of the adjacent organs was present. The whole picture can be explained only by the assumption of a hematogenous origin of these ulcers. A description of a similar case of a fatal hemorrhage in hematogenous gastric tuberculosis could not be found in the literature.

WATERHOUSE-FRIDERICHSEN SYNDROME. E. E. AEGERTER (by invitation).

The Waterhouse-Friderichsen syndrome was first accurately described in the literature in 1901. Since that time it has been recognized as a disease entity in England and Germany. The symptoms include sudden onset, malaise, restlessness and often gastro-intestinal disturbances. These symptoms are followed shortly by lethargy, which rapidly deepens into coma. High fever, weak rapid pulse, intense cyanosis and purpuric hemorrhage into the skin are characteristic. The disease is usually fatal in from sixteen to twenty-four hours. Bilateral adrenal hemorrhage of massive proportions is the most common finding post mortem. The etiologic basis is probably a fulminating meningococcemia. The suggested therapy includes the administration of extract of adrenal cortex, epinephrine hydrochloride, sodium chloride, fluids, antimeningococcic serum and dextrose and blood transfusions.

DISCUSSION

MILTON HELPERN: The title of the paper, I think, is misleading. In the past year among the cases of sudden death in which autopsies were performed in the Medical Examiner's office there were eight cases of fulminating epidemic meningococcic meningitis. In these cases the typical appearance of severe spotted fever was presented on external examination and autopsy revealed marked congestion of the brain with and without grossly visible suppuration of the meninges. In all of these cases there were extensive hemorrhages into the adrenal glands. On the other hand, there have been other cases of meningococcic meningitis in which quite as striking skin manifestations were found externally, but in which there were no hemorrhages into the adrenal glands. I cannot see why the cases presented tonight should be labeled with the name of the Waterhouse-Friderichsen syndrome rather than with that of epidemic meningococcic meningitis, since hemorrhages into

the adrenal glands may be a definite manifestation of severe meningococcic infection. I have seen similar hemorrhages into the adrenal glands in cases of post-abortion sepsis obviously not caused by the meningococcus. In the first case presented, gross hemorrhages into the adrenal glands were described, but in the second the organs were described as congested.

ALFRED PLAUT: Years ago one occasionally saw unexplained bilateral adrenal hemorrhage in children. I wonder if that also was due to fulminating meningococcic infection. Perhaps the meningococcemia was overlooked.

ANTONIO ROTTINO: Last spring I had an opportunity to perform an autopsy in one case, and in another the body was sent to the Medical Examiner's office for autopsy. In one case Meningococcus was isolated from the blood stream and in the other from the spinal fluid. In the case in which Dr. Helpern performed the autopsy massive hemorrhages were observed in the adrenal gland, and in the other case, microscopic hemorrhages. We dismissed the cases as examples of simple fulminating meningitis without trying to classify them as instances of the Waterhouse-Friderichsen syndrome.

IRVING GRAEF: Were microscopic sections of the brain made?

E. E. AEGERTER: Yes. They showed typical congestion.

I agree with Dr. Helpern that the name "Waterhouse-Friderichsen syndrome" should be dropped. I do not altogether agree, however, that the condition should be called fulminating meningitis if there is no meningitis. When there are obvious infection of the blood stream and marked adrenal hemorrhage the condition should be called fulminating meningococcemia. Since the symptoms following infection of the blood stream with Meningococcus parallel closely what one may assume are symptoms in destruction of the adrenal cortex, I do not see how one can be sure that destruction of the adrenal cortex does not enter as a cause of the symptoms and even as a cause of death. My only contention is that if such is the case the therapy should be changed and the patients provided with sodium chloride and fluids in the hope of holding them over until, with serum, the infection may be allayed. This conception may not be probable, but it is at least rational.

EPITHELIAL INVASION IN THE POSTERIOR LOBE OF THE HYPOPHYSIS. ALFRED PLAUT.

Seventy-six hypophyses from unselected patients whose blood pressure readings were available have been examined. At least twelve different levels were studied. The sections were embedded in paraffin and stained with hematoxylin and eosin. In many cases a large number of sections were available; there were some series. No parallelism could be found between the blood pressure and the epithelial invasion in the posterior lobe. In the six patients whose blood pressure was highest the basophilic invasion in the posterior lobe was, respectively, as follows: very much, very little, little, slight, much, moderate. The greatest invasion was found in a 60 year old patient with uremia. On the other hand, in a patient with a blood pressure of 300 the posterior lobe of the hypophysis showed very few basophilic cells.

A study has been made of the epithelial invasion in a large number of hypophyses, from most of which hundreds of paraffin sections were available. In no case was the posterior lobe found entirely free from epithelial cells. Even in the hypophyses from new-born infants serial sections and careful search always led to the detection of single basophilic epithelial cells. Only occasionally, non-basophilic epithelial cells were found. The overwhelming majority of the invading cells were characteristic granular basophilic cells. I use the old nomenclature of chief cell, basophilic cell and eosinophilic cell, and for the differentiation of the three types I am satisfied with a well differentiated strong hematoxylin-eosin stain. In the hypophysis of the new-born infant, the continuity between the epithelial lining and the invading cells is easily demonstrated. The single cells tend to migrate along capillaries. In suitable sections the origin of the invading cells can

be traced to the Erdheim glands as well as to the epithelial lining of the remnants of the hypophyseal cleft. The Erdheim glands communicate with the lumen of the cleft or its remnants. Occasionally, in the cells of the Erdheim glands small secretory granules are seen. No basement membrane is seen in the lining of the hypophyseal cleft. The epithelial cells which line the cleft vary from flat or low cuboidal undifferentiated elements to the fully differentiated large granular basophilic cells. Only fully differentiated cells are seen invading. In one case I have been able to see the epithelial cell receding from the epithelial lining. The empty space left in the single row of lining epithelial cells is distinctly seen in these sections, and the shape of the receding cell as well as the arrangement of its protoplasm is highly suggestive of ameboid motion.

A further source of the epithelial invasion lies in epithelial tissue extending in some instances far under the capsule of the posterior lobe. Such tissue may appear rather undifferentiated or it may show characteristic basophilic cells. Many different phases of disintegration of epithelial cells are observed in the posterior lobe, but it is not possible to trace definitely the relation between the disintegrating epithelial cells and the varying so-called colloid and hyaline formations or the pigment in the posterior lobe. There is a definite topographic and quantitative relation between the epithelial invasion and the pigment. In one specimen, in the epithelial cells which lined one of the glandular structures in the region of the pars intermedia, pigment was found which, in its aspect and its microchemical reactions, was identical with the pigment of the posterior lobe. These observations prove at least that the pigment may arise from the epithelial cells. Some of the irregular large cells in the posterior lobe leave one in doubt whether they are epithelial or neuroglial. At present, the following working hypothesis presents itself: The pigment in the posterior lobe of the hypophysis is probably derived from disintegrating invading basophilic cells and is then taken up by neuroglial elements of the posterior lobe.

The observation that the epithelial cells in the posterior lobe come from the adenohypophysis and migrate actively seems indisputable. In none of the many specimens examined was the impression given that epithelial cells are situated in the posterior lobe from the beginning, forming a kind of heterotopy, as Dieckmann suggested. The academic question whether one shall call the invading cells cells of the anterior lobe or cells of the pars intermedia will not be discussed here.

I still do not believe that the epithelial invasion of the posterior lobe has to be regarded as the morphologic basis of an important function. The proof of the parallelization of the morphologic changes observed and function in the hypophysis and in the hypophysis-interbrain system is utterly incomplete. Most of the venous pathways from the hypophysis do not reach the brain. Lymph spaces never have been demonstrated in the anterior lobe. The hypophyseoportal circulation, as described by Popa and Fielding, does represent a pathway from the hypophysis to the interbrain. Its constancy and quantitative importance must be established by further study. The posterior lobe was not found so poor in capillaries as the textbooks state. Conclusions drawn from studies of the vascularization of a secreting organ should be accepted with great caution. The pars intermedia, for instance, in many animals contains few blood vessels, but nobody doubts its function in these animals.

The main riddle lies in the discrepancy between the potency of extracts of the posterior lobe and the absence of secreting tissue in the lobe. The possibility may be considered that the complicated neuroglial elements of the posterior lobe have a secretory function or some unknown function similar to what is generally called secretion. The histologic pictures of the interbrain gland in man and many animals hardly admit of any interpretation other than that of secretion in the ectoblastic central nervous tissue. (Lantern slides.)

DISCUSSION

ROBERT A. MOORE: In connection with that part of Dr. Plaut's paper concerned with hypertension and the epithelial invasion of the posterior lobe of the

hypophysis, I should like to discuss some observations made by Dr. Robert J. Parsons, working in the New York Hospital—Cornell University laboratories. In two years he secured 110 pituitary glands. These were sectioned at three levels according to the technic of Cushing. Each section was stained with hematoxylin and eosin, and Mallory's stain was used for sections of the anterior lobe on which differential cell counts were to be made. Cell counts were made only in a few selected cases. Particular attention was given to the matter of basophilic invasion of the posterior lobe, and the invasion was classified as 0, 1, 2, 3 and 4 plus on the basis of the three levels. The figures for the blood pressures were secured from the clinical charts, and the averages were taken. The sex and age were recorded. It was felt that in correlation the most logical method of approach was to calculate the correlation coefficient between the three sets of figures for age, blood pressure and invading cells. By that method the zero order and first order correlations could be determined and one factor eliminated. There was a positive correlation with a probable error of about 4 between basophilic invasion and age. The probable error of the correlation between blood pressure and basophilic invasion was less than 1—in other words, an insignificant correlation—so that on the basis of these 110 glands Dr. Parson's results are in agreement with those of Dr. Plaut and indicate that there is no correlation between basophilic invasion and blood pressure. There is, however, a correlation between invasion and age.

Irving Pardee (by invitation): I cannot let Dr. Plaut's statement about the secretory or the possible secretory activity of glial tissue go unquestioned. In the first place, one knows that the posterior lobe of the pituitary does not grow from the oral cavity. In other words, the anterior lobe has its origin from the upper part of the oral cavity, and the posterior lobe has its origin from the base of the brain, a downward growth. These two parts join and form the pituitary gland. The posterior lobe is therefore composed of glial tissue, of neural tissue, and so far as I have been able to read in the literature and as far as my knowledge of the functions of glial tissue goes I have never conceived it possible that glial tissue has any secretory function. It may have some chemical action, to be sure; one does not know enough about that to say. But I think it is more than one should expect of glial tissue to expect it to secrete a hormone. If there is an invasion of the posterior lobe by basophilic cells the question whether they come from the anterior or from the intermediate lobe is of interest. One is fully cognizant that the posterior lobe has intimate glial relationships with the hypothalamic region, and one also knows that the hypothalamic region has in it nuclei the functions of which are vegetative. One also knows that the posterior lobe has functions which are vegetative. Whether the action of the hypothalamus conditions that of the posterior lobe or whether the action of the posterior lobe conditions that of the hypothalamus I am not prepared to say, but there is so intimate a connection between these two structures that functions formerly believed to belong to the pituitary are now being considered as having their centers in the hypothalamus, such as water control and fat control, and some of the German experimenters have gone so far as to place a center of sexual control there; so I think it would be too bad to leave the slightest impression in any one's mind that the glial tissue of the posterior lobe may have a secretory function. There are plenty of glands in the brain, fourteen different kinds, with which I am sure Dr. Plaut is familiar, though he mentioned only one, and these fourteen different kinds of glands have functions, some of which are known and some of which are not known.

The question of the hyaline bodies is of interest because no one knows where they come from and no one knows where they go. They have never been found coursing up into the brain, as Cushing so hopefully tell us. One only knows that if a clip is put on the pituitary stalk they are found concentrating around that clip. What that means no one knows, but at least, so far as I can see, the hyaline bodies are not structures to which one can attribute any special secretory function.

ALFRED PLAUT: I am glad that the study of the hypophyses at Cornell Medical School led to the same results as the present study did. As to the technic, I should like to warn against conclusions drawn from the examination of a few sections only. There probably is no posterior lobe in which one or another invading epithelial cell can not be found if a sufficient number of sections are examined.

I anticipated opposition to my statement about the secretory-like function of the neuroglia in the posterior lobe. There may, after all, be some function intermediate between what one calls secretory and what one calls nervous function. Since there probably is some chemical basis of nervous function, such an assumption does not seem to me unwarranted. The fact that the posterior lobe is derived from the ectoblast does not preclude its having secretory function. It seems to me difficult to interpret the histologic observations in the posterior lobe of the hypophysis and in the "interbrain gland" unless one assumes that there is either secretion or a similar process.

THE PITUITARY GLAND IN ANENCEPHALY. D. MURRAY ANGEVINE.

Twelve anencephalic monsters are described. The maternal history was obtainable in regard to ten of them. In regard to six of these ten definite clinical diagnosis of hydramnion was made and was confirmed by x-ray picture in each instance.

In only two monsters could a brain tissue be recognized grossly as such. Sections of the hemorrhagic tissue over the calvarium which were made in five instances revealed a considerable amount of vascular hyperplastic choroid plexus. It is suggested that secretion of spinal fluid in the absence of surrounding brain may be of some importance in explaining the hydramnion.

In two of the monsters the pituitary gland was recognized as a gross structure. In order to determine its presence accurately the entire region of the sella turcica, including the pharynx, was removed in one block and decalcified, and several sections were cut. Similar sections were prepared from normal fetuses. The anterior lobe was found in every instance; in two cases it was very small; in one case it was larger than in any of the normal pituitaries. In three cases the pars intermedia was seen; in two of these, a small pars nervosa was present; in the other, it could not be determined with certainty. Microscopically the anterior lobe was more vascular and showed considerably more acidophilic cells than the normal.

The adrenal glands were found in all the eleven cases in which they were sought. They were usually small, their combined weights varying from 0.2 to 1.9 Gm., with one exception in which the weight was 6 Gm. The cortex and medulla were sharply demarcated without any intermediate boundary zone. The heavier adrenals were found in monsters that weighed less than 2,000 Gm.; in no monster weighing more than this did the combined weight of the adrenal glands exceed 0.6 Gm. This indicates that at some time during development the adrenal glands are larger than at term, and therefore the small adrenal gland should be considered atrophic rather than aplastic, as it is usually described.

No correlation between the size of the pituitary and that of the adrenal gland could be establshed, nor was there any direct relationship between the amount of brain tissue and the size of the adrenal glands.

The thyroid glands of the monsters contained colloid in smaller amounts than did those from the normal fetuses of the same weight. The thymus glands of the anencephali in comparison revealed no differences from those of the normal fetuses. Hydronephrosis was noted in three of ten cases.

DISCUSSION

ALFRED PLAUT: Was the posterior lobe always entirely absent? In our last anencephalus, a considerable amount of posterior lobe was present.

D. MURRAY ANGEVINE: I found the posterior lobe with certainty in two cases, and its presence in another was questionable. A good many observers have

found it. The posterior lobe has been present in more than 20 per cent of the cases that have been reported.

ANTONIO ROTTINO: I cut the pituitary of an anencephalic monster serially, cutting practically the whole gland, and in none of the sections was I able to find a posterior lobe.

CHICAGO PATHOLOGICAL SOCIETY

PERCIVAL BAILEY, *President*

Regular Monthly Meeting, Dec. 9, 1935

EDWIN F. HIRSCH, *Secretary*

CHRONIC OCCLUSION OF THE PORTAL VEIN. J. P. SIMONDS.

A case of chronic occlusion of the portal vein by an old organized and canalized thrombus is described because only six cases of this condition have been reported in English, and because the reports appeared in 1867, 1868, 1882, 1904 and 1928. The report is also made because the condition is rarely diagnosed clinically, being usually mistaken for cirrhosis of the liver, Banti's disease or ulcer of the stomach, and because, in this case, an unsuspected and very unusual collateral circulation defeated the anticipated result of a successful splenectomy which, in any other case, would have been the logical treatment.

An obese white woman, 34 years of age, suffered from epigastric pain and repeated gastric hemorrhages at intervals of three or four months for two years. The spleen was palpable. These hemorrhages had not induced anemia, for the red cell count one month after the last hemorrhage was 4,900,000. The platelet count ranged from 86,000 to 104,000 before splenectomy to 190,000 three days afterward. The leukocyte count was 5,700 before operation. Jaundice and ascites were absent. The clinical diagnosis was: thrombocytopenic purpura, splenomegaly and gallstones.

The spleen, after the escape of much blood, weighed 397 Gm. It showed diffuse fibrosis of the pulp but not the fibro-adenia of Banti's disease.

Autopsy revealed obliteration, canalization and partial calcification of the greater part of the main stem of the portal vein. At the hilus this condition gave place to a cavernous transformation or replacement of the vein, which extended for a short distance into the liver. No satisfactory explanation of the gastric hemorrhages was found. Varices in the lower end of the esophagus, the usual source of hemorrhage in cases of this type, were not present. The collateral circulation, which was so adequate that no ascites ever developed, was by way of huge varicose venous connections between the splenic and left renal veins. This exceedingly rare and unsuspected collateral circulation defeated the favorable results to be expected from splenectomy. Removal of the spleen and ligation of the splenic vein blocked the only open channel through which blood from the stomach and intestines could return to the general circulation.

This report is based on a study of this case and ninety-four instances collected from the literature. Some of the recorded reports of cases are too meager to be of much value, and this fact is taken into account in analyzing the data. These cases may be divided into two groups: those in which the portal vein was replaced by fibrous tissue with little or no canalization and those in which the portal vein and/or its immediate vicinity was transformed into a cavernous mass of tortuous blood channels. This classification is significant because the type of change has an effect on the clinical picture, influences the establishment of a collateral circulation and is a factor in determining the cause of death.

Ascites and hematemesis are more frequent and more severe in group 1. A centrifugal type of collateral circulation by way of esophageal varices is almost

invariable in group 1, while a centripetal collateral circulation through the cavernous tissue and the accessory portal veins of Sappey characterizes group 2. Hemorrhage is the most common cause of death in group 1; infarction of the intestines, in group 2.

In the literature have been found reports of only six cases with a collateral circulation similar to that in this case, namely, from the splenic to the left renal vein.

The complete report will appear in the *Archives of Surgery*.

DISCUSSION

WILBUR POST: Was a clinical diagnosis of portal thrombosis made in any of the six cases as in yours?

J. P. SIMONDS: No.

CYSTICERCUS CELLULOSAE OF THE HUMAN BRAIN. PAUL C. BUCY and CLAY G. HUFF.

Cysticercus cellulosae (Taenia solium) is at present an uncommon cause of cerebral disorder in this country. A case is presented because of the difficulty encountered in arriving at a correct diagnosis, which was not made until the necropsy was done, and because of the unusual nature of one of the specimens obtained.

A stenographer, aged 25 years, entered the University of Chicago Clinics on Aug. 26, 1931, stuporous and unresponsive. She had seemed in excellent health until the latter part of July 1931, when she complained of numbness and tingling in the arm, neck and face (the side not specified). On August 16 she had a severe frontal headache. This grew worse and on August 18 was associated with vomiting. These symptoms, with dizziness, confined the patient to bed; she became dull and lethargic, and by August 22 it was difficult to arouse her. She was thought to have "sleeping sickness," a diagnosis not concurred in by all. After examination at the clinic, she was thought to have a rapidly growing glioma of the left frontal lobe. On August 28 the left frontal lobe of the brain was explored but no tumor or other abnormality was found except a gray region 5 mm. in diameter on the surface of the frontal lobe. The wound was closed after a subtemporal decompression had been made. The gray mass in the meninges proved to be chronic granulation tissue; its characteristics were not further identified. The patient recovered slowly from the operation, but severe right hemiparesis and complete expressive aphasia persisted. Roentgenotherapy had no effect, and she was discharged unimproved on November 24. Her condition remained stationary; occasionally there were convulsive seizures of the right side. She returned to the clinic on Sept. 12, 1935. Since September 1934 there had been attacks of vomiting, increasingly severe and more frequent. The tissues opposite the decompression bulged, and about a week prior to readmission a small amount of cerebrospinal fluid escaped from the wound. The skin about the opening became red, and the fluid was purulent. Fluid aspirated from the bulging tissues was purulent and culturally contained gram-negative bacilli. The patient died on Sept. 16, 1935.

An examination of the body revealed hypostatic pulmonary edema and pneumonia, acute ulcerative esophagitis, fatty changes of the liver, brown atrophy of the myocardium, fibrocaseous tuberculosis of the left lung and of the lymph glands at the hilus and small cysts in the mammary glands. Parasites were found only in the brain.

The left hemisphere of the brain was reduced to a large sac by distention of the lateral ventricle. The brain substance formed a thin friable wall about the ventricle. There was considerable purulent material within the ventricles and over the surface of the brain. In the right superior frontal convolution was a translucent cyst about 12 mm. in diameter. Another was in the meninges just to the

left and anterior to the pons varolii; another, in the region of the third ventricle; one, under the right temporal lobe, and four large ones were within the left lateral ventricle.

Microscopic examination revealed marked purulent meningitis. Cysts satisfactory for fixed preparations were not obtained, as the ones best preserved were saved for more careful study. One cyst, which was sectioned in paraffin and stained with hematoxylin and eosin, had a thick connective tissue wall. The contents consisted of a mass of débris with numerous cholesterol slits. About the wall of the cyst were foreign body giant cells, and the surrounding brain tissue showed gliosis, connective tissue proliferation and mild lymphocytic infiltration.

Four of the cysts discovered at autopsy were examined, two in the unfixed state, one by artificial digestion after fixation, and one by clearing with sodium hydroxide after fixation. The latter was a normal cysticercus (Cysticercus cellulosae larval form of Taenia solium) bearing a double row of twenty-four characteristic hooks on the rostellum. The other three were pronounced abnormal or malformed cysticerci. The large one from the region of the third ventricle was approximately 3 cm. in diameter; it had a thin wall and a structure suggesting a scolex but lacked a rostellum and hooks. The smaller cyst, fixed, dissected and then submitted to artificial digestion, also lacked hooks. The small cyst examined in the unfixed condition was normal in every respect except in the number of hooks on the rostellum. Only eight hooks were present, whereas the normal number is from twenty-two to thirty-two. Although malformations of the cysticerci of this species are known to include the absence of the rostellum and hooks (as in our specimens) and double formation with six suckers instead of four, we have been unable to find any record of a cysticercus with only eight hooks.

Cysticercosis in man has been known since the middle of the sixteenth century. It is acquired through contamination of food with feces containing the ova of Taenia solium or by direct transfer of these ova to the mouth. Up until the middle of the nineteenth century about 2 per cent of all autopsies in Berlin showed cysticerci, but there has been a rapid decline in cysticercosis since then. The condition is rare today. The order of frequency in the various organs is: brain, eye, muscular system, heart, subcutaneous connective tissue, liver, lungs and abdominal cavity. It is well known that the malformations in cysticerci are most frequent among those found in the brain, particularly at the base of the brain.

DISCUSSION

PETER BASSOE: Was there eosinophilia of the blood?

A. A. GOLDSMITH: Were there any findings in the eyes? Eosinophilia is common with round worm but rare with flat worm infestation.

P. C. BUCY: The only ocular changes were choked disks. There was no eosinophilia of the blood.

DEATH AS A CONCEPT OF ENERGY. W. F. PETERSEN.

When a comparison is made of the curves of the daily deaths in Milwaukee, Chicago and Detroit (crude death rates) a series of major waves are to be observed that are synchronous for the three cities and are similar in their relative amplitude and general character. Examined with relation to the meterological associations, it is found that these accentuations of deaths in the population are associated with or follow periods of polar infall, and this accounts for the similarity in the cities examined, which lie in the pathway of the circumpolar circulation.

The reason for this phenomenon is to be sought in the greater demand on energy occasioned by the polar episodes, death merely revealing the deficiency in members of the community whose energy is inadequate to meet this demand. The effect is evident irrespective of the particular disease which may dominate the terminal picture.

DISCUSSION

I. PILOT: Clinical observations verify the statements of Dr. Petersen. Thus, during the season for pneumonia several patients die at the Cook County Hospital during a given night and then two or three days elapse before other deaths occur. There may be an interval when no patients with acute appendicitis are admitted and then several are admitted in a single day.

A. A. GOLDSMITH: Is there any way of stabilizing these atmospheric conditions and thus safeguarding the patient?

W. F. PETERSEN: These phenomena of the death rate concern increased pressor episodes. I doubt if conditions can be stabilized. Air-conditioning now can be extended to only a small part of the population, and patients indoors in bed manifest reactions although they are not subjected to the extreme of variations of external temperature and humidity. Possibly any one of several stimuli may arouse a sequence of reactions. This is difficult to prove. Variations in atmospheric pressure would be difficult to control. Patients transferred to stable climates live longer than those subjected to great atmospheric changes.

ATHEROSCLEROSIS: ITS INCIDENCE AND CONSEQUENCES IN A THOUSAND NECROPSIES. NATHAN S. DAVIS III.

An analysis of the records of a thousand consecutive complete necropsies was undertaken to determine whether information regarding the incidence of atherosclerosis and of its consequences might be of more value than that gained from clinical studies and mortality statistics based on death certificates. It seems that this method of approach, particularly if pathologists will note as a routine changes in arteries other than the aorta and coronary arteries, may yield more accurate statistics than others that have been tried.

The study of a thousand cases may furnish fairly accurate information as to gross incidence but cannot furnish satisfactory data as to age of incidence, as the number in each five year group is insufficient. However, the uniformity of the curves presented suggests that atherosclerosis may appear in childhood, rapidly becomes more common and extensive in persons over 39, and is almost always present in those over 69. This study further suggests that the onset of atherosclerosis occurs about ten to twenty years before there is much scarring of the myocardium, before there is much calcification of the lesions, and before it becomes important as a cause of death. In this series it is the etiologic factor in some 30 per cent of the primary and contributory causes of death in those 45 years old and over, and in some 55 per cent of the causes in those 65 years old and over. Its incidence as the etiologic factor of the primary cause of death is greater than that of carcinoma in those 45 years old and over and less in those 44 years old and under. Atherosclerosis appears to be the most common pathologic observation in those 45 years old and over, and the pathologic changes secondary thereto are an increasingly frequent cause of death, especially in the older age groups.

DISCUSSION

A. LEVINE: At the Cook County Hospital the results of four hundred and fifty autopsies on patients aged 1 year and upward were analyzed. In these examinations more arteries than are usually inspected were studied. The results are about the same as those reported here. At about the age of puberty there is some increase in arteriosclerosis and then the condition disappears until the ages from 20 to 30 years.

Book Reviews

Immunology. By Nobel Pierce Sherwood, Ph.D., M.D., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kan. Price, $6. Pp. 608, with 27 illustrations and 8 colored plates. St. Louis: C. V. Mosby Company, 1935.

According to the preface, this book is intended for medical and other students who have had adequate training in bacteriology and chemistry. It aims to present "the underlying principles involved in infection, resistance and diagnostic laboratory tests." The first four chapters are devoted to infection and infectious agents, host-parasite relationships, anatomic and physiologic factors in infection and resistance of the individual, inflammation and tissue immunity. Then comes the consideration of theories of immunity; antibodies in diagnosis; blood groups, haptens and heterophile antigens; precipitins; toxins and antitoxins, and specificity. A chapter on colloids is then introduced for the benefit of students who are not familiar with colloid chemistry. Next to be considered is the mechanism of antigen-antibody reactions: agglutination, opsonification, and complement fixation, with a description of the technic and clinical applications, including precipitin tests in syphilis. The last chapters contain much detail concerning hypersensitiveness and its varied manifestations. At the end of each chapter are lists of appropriate references, mostly to recent publications. There are good author and subject indexes. The illustrations, eight plates in colors and twenty-seven figures, are good. The publisher's work and the proofreading are well done. A few mistakes in spelling may be noted: Abels for Abel, page 20; C. diphtheria for C. diphtheriae consistently throughout (why not simply diphtheria bacillus?); Hohnes for Löhnis (?), page 29; Küpfer for Kupffer, page 92; McCordeck for McCordock, pages 109 and 110; B. dysenteria for B. dysenteriae, page 204; Cl. botulinus for C. botulinum, page 24 and in the index; Well's for Wells' and Andrew's for Andrews' in the subject index. The book covers a large field and contains much information, but the presentation in large measure takes the form of separate abstracts of individual articles without coordinating comments. Opinions of authors may be given without any discussion of the foundation on which these are based. In many cases altogether too many scattered details are introduced without discrimination, and the student would not be able to separate the wheat from the chaff. Fundamental work hardly receives adequate consideration. Vaccination against smallpox is not described in detail; allergy in smallpox and vaccinia is not considered; the Pasteur treatment of hydrophobia seems to have escaped notice. Sometimes the scattered notes and abstracts fail to give a correct idea of the present situation.

Taken as a whole, the book must be evaluated as a large, fairly well classified and well indexed collection of notes and abstracts rather than as a systematic textbook in the usual sense. The development and state of the knowledge in the field of immunology are not presented systematically and discriminatingly with appropriate and comprehensive generalizations to meet adequately the needs of the student. But the work contains much of the material needed for a good textbook.

Human Pathology: A Textbook. By Howard T. Karsner, M.D., Professor of Pathology, Western Reserve University. With an Introduction by Simon Flexner, M.D. Fourth edition, revised. Price, $10. Pp. 1,015, with 18 illustrations in color and 443 in black and white. Philadelphia: J. B. Lippincott Company, 1935.

The author who sets for himself the task of writing a textbook that shall cover both the general and the systemic subdivisions of pathology has a big job on his

hands. Limitations of space make necessary the judicious omission of subjects of minor importance and a succinct discussion of what is included. Karsner devotes 428 pages to general pathology and 586 pages to systemic pathology—probably as equable a division as can be made.

The individual teacher may be permitted to determine for himself the sequence in which the general pathologic processes shall be considered. The sequence used by Karsner is that which seems to lead the student most easily from the relatively simple subject of pathologic pigmentation to the more complicated fields of inflammation and tumors.

In this new fourth edition more than three hundred new references have been added. Although most of the references are properly to the English literature readily accessible to the student, one is glad to find included a reference to Klinge's work on rheumatic infection. The chapters on tumors, the hematopoietic system and the ductless glands have been revised.

The book is written in a simple style suitable to the average second year medical student. The better than average student will make use of the bibliography at the end of each chapter and should read some more philosophic work, like Adami's "Principles of Pathology" or Oertel's "Outline of Pathology." The reviewer wishes that writers in English might break away from the use of the suffix "ata" in the plural names of neoplasms, but this is a purely personal reaction.

Of the numerous excellent illustrations in black and white only a few are not original, and most are from drawings. The fly-leaf states that there are 443 black and white illustrations; the last one is numbered 433.

The book fulfils well its purpose, that of a text to be used in the regular course in pathology. The practitioner, who should return to his textbook of pathology more often than he does, will find the subject matter covered in sufficient fulness to meet his needs.

Books Received

MODERN CRIMINAL INVESTIGATION. Harry Söderman, D.Sc., Head of the Institute of Police Science, School of Law, University of Stockholm, Sweden, and John J. O'Connell, Deputy Chief Inspector, New York City Police Department and Dean of the Police Academy. Price, $3. Pp. 461, with 110 illustrations. New York: Funk & Wagnalls Company, 1935.

THE STANDARDIZATION AND ESTIMATION OF VITAMIN A. REPORTS ON BIOLOGICAL STANDARDS. Edited by E. Margaret Hume and Harriette Chick. Medical Research Council, Special Report Series, no. 202. Price, 1 shilling. Pp. 61. London: His Majesty's Stationery Office, 1935.

THE SOURCE OF INFECTION IN PUERPERAL FEVER DUE TO HAEMOLYTIC STREPTOCOCCI. Dora C. Colebrook. Medical Research Council, Special Report Series, no. 205. Price, 1 shilling, sixpence. Pp. 99. London: His Majesty's Stationery Office, 1935.

BIOLOGISCHE UNTERSUCHUNGEN ÜBER FARBSTOFFE. Dr. Iwao Matsuo, Professor der Medizin der Kaiserlichen Universität zu Kyoto. II Band. Pp. 551. Kyoto, 1935.

POST MORTEMS AND MORBID ANATOMY. Theodore Shennan, M.D., F.R.C.S. (Edin.), Professor of Pathology in the University of Aberdeen. Third edition. Price, $9. Pp. 716, with 241 illustrations. Baltimore: William Wood & Company, 1935.

ANNUAL REPORT OF THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE OF THE UNITED STATES FOR THE FISCAL YEAR 1935. Cloth. Price, 75 cents. Pp. 158, with 3 illustrations. Washington: United States Government Printing Office, 1935.

THIRTY-THIRD ANNUAL REPORT, 1934-1935, OF THE IMPERIAL CANCER RESEARCH FUND. Under the direction of the Royal College of Physicians of London and the Royal College of Surgeons of England. Pp. 35. London: 1935.

REPORT OF THE SECRETARY OF THE SMITHSONIAN INSTITUTION AND FINANCIAL REPORT OF THE EXECUTIVE COMMITTEE OF THE BOARD OF REGENTS, 1935. Pp. 90, with 2 plates. Washington, D. C.: Smithsonian Institution, 1936.

RHEUMATISMUS UND RHEUMATISCHE ERKRANKUNGEN. Prof. Dr. Siegfried Gräff, Leitender Oberarzt am Pathologischen Institut des Allgemeinen Krankenhauses Barmbeck in Hamburg. Price, 5 marks. Pp. 82, with 26 illustrations. Berlin: Urban & Schwarzenberg, 1936.